



# Alzheimer's disease: A review of its visual system neuropathology. Optical coherence tomography—a potential role as a study tool in vivo

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Received: 25 April 2016 / Revised: 12 June 2016 / Accepted: 22 June 2016  
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**Abstract** Alzheimer's disease (AD) is a prevalent, long-term progressive degenerative disorder with great social impact. It is currently thought that, in addition to neurodegeneration, vascular changes also play a role in the pathophysiology of the disease. Visual symptoms are frequent and are an early clinical manifestation; a number of psychophysiologic changes occur in visual function, including visual field defects, abnormal contrast sensitivity, abnormalities in color vision, depth perception deficits, and motion detection abnormalities. These visual changes were initially believed to be solely due to neurodegeneration in the posterior visual pathway. However, evidence from pathology studies in both animal models of AD and humans has demonstrated that neurodegeneration also takes place in the anterior visual pathway, with involvement of the retinal ganglion cells' (RGCs) dendrites, somata, and axons in the optic nerve. These studies additionally showed that patients with AD have changes in retinal and choroidal microvasculature. Pathology findings have been corroborated in in-vivo assessment of the retina and optic nerve head (ONH), as well as the retinal and choroidal vasculature. Optical coherence tomography (OCT) in particular has shown great utility in the assessment of these changes, and it may become a useful tool for early detection and monitoring

disease progression in AD. The authors make a review of the current understanding of retinal and choroidal pathological changes in patients with AD, with particular focus on in-vivo evidence of retinal and choroidal neurodegenerative and microvascular changes using OCT technology.

**Keywords** Alzheimer's disease · Optical coherence tomography (OCT) · Retina · Choroid

## Introduction—Alzheimer's disease (AD)

Alzheimer's disease (AD) is a long-term progressive neurodegenerative disorder affecting the central nervous system (CNS). It is the most common cause of dementia, affecting about 6 % of the population aged over 65, and the clinical incidence doubles every 5 years after 65 years of age [1, 2]. Over 26 million people are estimated to suffer from AD, and this number is expected to quadruple by 2050 [3]. It is therefore a disease with a great social impact, leading to considerable impairment in quality of life for both patients, family members, and healthcare workers.

Its pathophysiology remains incompletely understood. The earliest AD pathological change in the CNS is the accumulation of amyloid  $\beta$  ( $A\beta$ ), derived from abnormal processing of amyloid precursor protein (APP). This process begins approximately 10 years before the onset of the clinical syndrome of dementia, which is characterized by a constellation of symptoms and signs manifested by difficulties in memory, disturbances in language, and psychological and psychiatric changes including behavioral disturbances, executive dysfunction, and impairment in activities of daily living [1, 4]. Clinical progression shows great variability among patients.

Mild cognitive impairment (MCI) is an intermediate state of cognitive function between normal aging and early dementia, in which patients may have one or more cognitive domains

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affected, without impairment in activities of daily living. It is considered a risk factor for Alzheimer's disease, with variable progression to AD [5].

### Visual changes in AD patients

Visual symptoms are frequently among the earliest symptoms in patients with Alzheimer's disease, and visual function is affected in most patients with AD, contributing to further impairment in quality of life.

There are a number of changes in visual function in AD patients including visual field defects, predominantly in the inferior hemifield, abnormal contrast sensitivity, and abnormalities in color vision, depth perception, and visual sensitivity to motion [6]. Other psychophysiological changes such as visual acuity and pupillary changes have been studied in patients with AD, with conflicting findings.

In addition, more complex visual symptoms may arise early in the history of AD, including visual memory deficits and visual hallucinations [7, 8].

However, the results of visual tests are dependent on the patient's understanding, memorization, vigilance, and compliance to the rules and the test instructions, which depends on the cognitive status of each patient. The ability to cooperate in some visual tests can be affected additionally by ocular motor abnormalities that may be present in patients with AD, such as slower saccadic movements and changes in smooth pursuit movement [9, 10]. Some of this data may thus be the result of poor compliance related to the cognitive status rather than the result dysfunction of the visual pathways [11].

### Neuropathology of the visual system in AD

The two most important neuropathological features of AD are cerebral A $\beta$ -amyloid neuritic plaques in neocortical terminal fields, and neurofibrillary tangles (NFTs) containing phosphorylated tau protein [12–14] initially in medial temporal-lobe structures and later in many forebrain and midbrain areas. Microvascular amyloid deposition (amyloid angiopathy), granulovacuolar degeneration, loss of neurons and white matter, synapse loss, gliosis, inflammation, and oxidative damage are other pathological changes present in AD [12–15].

### AD pathological changes in the posterior visual pathway

Neurodegenerative changes have been demonstrated in most visual systems in AD. In fact, degenerative changes in the visual pathways occur early in the disease process of Alzheimer's, even before the onset of clinical symptoms of dementia [15, 16].

The visual cortex is relatively spared, and visual association areas (V2, V3) are more affected than primary visual

cortex (area V1). In the primary visual cortex, the density of neuritic plaques and NFTs has been shown to be significantly greater in the cuneal gyrus compared to the lingual gyrus. This may account in part for the predominantly inferior VFDs in patients with AD [9].

Degeneration of lateral geniculate nucleus (LGN) has been documented in patients with AD [17]. Couser and Bernstein (2014) observed the presence of AD-related markers in the lateral geniculate nucleus (LGN), proposing that AD-related changes take place in this structure very early in the disease process [18].

Neurodegenerative changes also occur in the suprachiasmatic nucleus (SCN) [19]. This hypothalamic region is involved in sleep-wake circadian rhythm, receiving direct input from RGCs via the retino-hypothalamic tract. Degeneration of the SCN may account for the sleep disturbances found in patients with AD. Regarding sleep disturbances in AD, it is of note that recent studies documented impairment of melanopsin RGCs (m-RGCs) in the retina of patients with AD. m-RGCs are a population of RGCs (1–2 % of total RGC population) involved in non-image-forming visual functions, including photoentrainment of circadian rhythms [20]. In this study, m-RGC density was significantly decreased in the AD group compared with controls, and remaining m-RGCs presented impaired function, altered morphology, and amyloid deposits in and around these cells. These changes occurred in m-RGCs even with normal RGC counts, suggesting these cells may be specifically affected in AD. Further studies are necessary to understand whether trans-synaptic retrograde degeneration due to SCN pathology might or might not play an additional role in m-RGC loss in AD.

Oculomotor brain nuclei, namely the superior colliculus (SC), are also affected by AD-related neurodegenerative processes [21]. This may account, at least in part, for the abnormalities in eye movements previously described. There appears to be also amyloid plaque deposition and NFTs in pulvinar nuclei of patients with AD, which may explain impaired visual attention in AD patients [22].

### Pathological changes in the retina and optic nerve

Visual defects in AD patients were initially thought to be solely due to parietal and primary visual cortex pathology. However, increasing evidence has demonstrated that anterior visual pathway degeneration also plays a role. Hinton et al. first provided histopathological evidence of optic neuropathy and degeneration of retinal ganglion cells (RGC) in patients with AD, with a reduced number of RGCs and reduced retinal nerve fibre layer (RNFL) thickness [23]. Later, post-mortem studies showed that degeneration of the ganglion cell layer (GCL) occurs preferentially in superior and inferior quadrants, as well as in the central retina, in particular the temporal foveal region [24, 25]. Initially, a preferential loss of magnocellular

RGC axons in the optic nerve was described [26], but other evidence suggests parvocellular RGC axon loss also takes place in AD [17]. Since then, pathology studies of AD patient's eyes have documented increased APP immunoreactivity, A $\beta$  and pTau deposits in the internal retinal layers (GCL, RNFL), retinal pigmentary epithelium, and retinal vasculature [27, 28], as well as reduction of choroidal thickness [29].

Animal models of AD have provided further insight regarding retinal changes in Alzheimer's disease. A study using mouse models of AD demonstrated that formation of neuritic plaques in the retina and choroidal vasculature occurs prior to their manifestation in the brain [27], and amyloid deposits were found in RNFL, RGCs, internal retinal layers, and even in the photoreceptor outer segments. Interestingly, this study also analyzed post-mortem human retinae of patients with AD, and observed a relation between severity of dementia and retinal amyloid plaque burden.

Evidence has emerged that degeneration of RGC dendritic processes in the internal plexiform layer (IPL) may take place before RGC loss, suggesting synaptic dysfunction may be an early change in the neurodegenerative process [30]. In addition, activated glial cells, hypertrophy of retinal pigmented epithelial cells, and choroidal inflammation have also been observed in the eyes of mouse models of Alzheimer's disease [3].

These neuropathological findings have raised the possibility that the changes in the retinae of patients with AD may be due to both direct retinal pathology and trans-synaptic retrograde degeneration. Trans-synaptic retrograde degeneration (TRD) of neurons is a process occurring after central nervous system lesions, in which degeneration of the axon proceeds towards the cell body, as opposed to anterograde (Wallerian) degeneration. This creates a hostile, neurotoxic environment that leads to secondary degeneration of neighboring neurons. TRD has been demonstrated in a number of neurological pathways; interest in TRD in the visual pathway has arisen since Van Buren et al. (1963) first observed atrophy of the right LGN and retinal ganglion cells (RGCs) following right occipital lobectomy in an adolescent monkey [31]. Later, pathology studies in humans with occipital lesions also revealed changes in LGN [32]. Clinical evidence further supported this hypothesis. Fletcher et al. (1988) described optic disc pallor and band atrophy in individuals with congenital occipital lesions. Initially it was believed that TRD in the visual pathway occurred only in individuals with congenital (prenatal) occipital lobe lesions [33], although recent studies have also provided evidence that TRD of RGC can also occur in patients with acquired occipital lobe lesions [34–36].

### Imaging of retina, optic nerve, and choroid in AD

In-vivo morphological studies have provided further evidence of both direct involvement of the retina and optic nerve head,

and TRD processes in patients with AD, as well as choroidal changes.

Initial in-vivo non-invasive studies of optical neuropathy in patients with Alzheimer's disease using fundus photographs showed retinal nerve fibre layer (RNFL) abnormalities, as well as macular changes and ONH abnormalities (increased cup-to-disc ratio and decreased neuroretinal rim) [37–39]. Increased cup-to-disc ratio has been reported to correlate with RNFL thinning in AD [40–42], and cup-to-disc ratio may be correlated with duration of disease [37]. This method, however, has certain disadvantages, as it is manual and highly subjective to each individual observer [41].

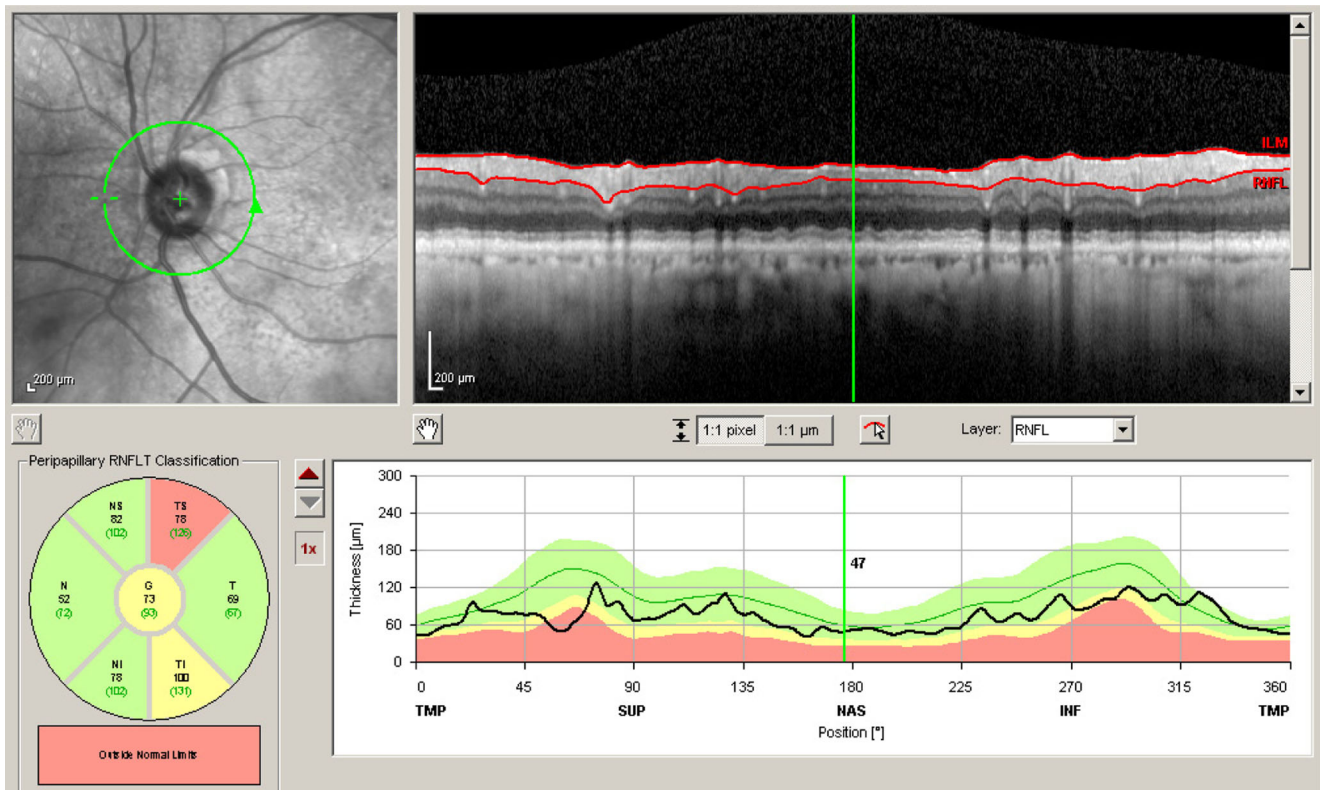
Later noninvasive studies of RNFL and ONH using scanning laser ophthalmoscopy (SLO) [42], and time-domain OCT (TD-OCT) studies confirmed the reduction in peripapillary RNFL thickness [40, 43–47]. In addition, in-vivo studies have shown reduced macular thickness and volume in patients with AD [44, 48–54].

Pathological changes in Alzheimer's disease not only involve neurodegeneration, but also the vasculature. The notion of AD as a disease of the neurovascular unit emerged from the findings of cerebral amyloid angiopathy, frequent focal changes in brain microcirculation, and especially because these vascular changes in AD are intimately associated with the typical neuronal degenerative changes [55]. Recent evidence has raised the possibility that the retinal microvasculature is affected in AD. Laser Doppler studies have shown altered retinal blood flow in patients with AD, although no correlation was found between RNFL thickness and retinal blood flow [45]. Two recent studies using retinal photography found retinal vascular abnormalities, including vascular attenuation, reduced branching pattern, and altered venular tortuosity [54, 56, 57]. According to the authors, these retinal vascular changes in AD may be correlated with the neocortical amyloid plaque burden [58] or may mirror the cerebral microvascular pathology [54].

The choroid also appears to be affected in AD. Atrophy of the choriocapillaris has been shown to occur with normal aging, and age-dependent amyloid accumulation in the choroid vasculature has been demonstrated in mice and also in transgenic mouse models of AD [59].

### Optical coherence tomography—a potential new biomarker for detection of AD

Early optical coherence tomography studies have shown peripapillary RNFL thinning in AD patients, although discrepancy has been found concerning which quadrants were most affected. More recent OCT studies have reported also macular changes in the ganglion cell complex (GCC), comprising the ganglion cell layer (GCL) and inner plexiform layer (IPL). Also, choroidal thickness [60] has been shown



**Fig. 1** Reduced RNFL thickness in Alzheimer's Disease, as measured by SD-OCT (Spectralis Heidelberg). In this case, diffuse RNFL thinning is documented, in particular due to thinning in the temporal superior and temporal inferior sectors

to be reduced in patients with AD, as measured by EDI-OCT Spectralis Heidelberg [61–63].

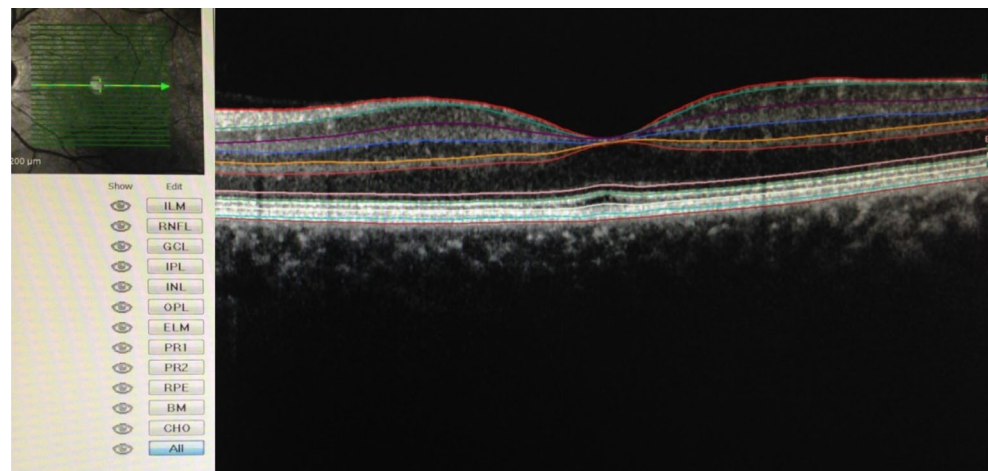
The evaluation of visual changes in AD patients has been difficult, due to difficulties in patient collaboration, and limitations in diagnostic exams to overcome these difficulties. These factors have long interfered with the interpretation of findings in these patients.

Nevertheless, results from the studies of retinal and choroidal changes in AD patients have raised the possibility that

OCT may be a non-invasive clinical biomarker for the early detection of AD. Retinal changes may be an early event in the course of AD, and retinal OCT may provide insights for assessing neurodegeneration in the brain [50].

OCT is a reliable non-invasive, trans-pupillary technique that provides high-resolution cross-sectional images of RNFL and macular volume, allowing visualization of axons of the central nervous system (CNS) and evaluation of RNFL thickness [39, 41]. Peripapillary RNFL thickness (RNFLT) is

**Fig. 2** Automatic segmentation of retinal layers in macular region as measured by SD-OCT (Spectralis Heidelberg)



**Table 1** Studies of peripapillary retinal nerve fibre layer thickness (RNFLT) in patients with Alzheimer's disease, as measured by optical coherence tomography

First author	Year of publication	Technology	Sample size (number of eyes)		Average peripapillary RNFLT thickness +/- SD (µm)	Peripapillary RNFLT quadrants most affected in AD patients	MMSE	Correlation between MMSE and RNFLT	Comments	
			Controls	Patients with AD						
Paris et al.	2001	TD-OCT	14	17	99.9 +/- 8.95	59.5 +/- 16.70	All sectors decreased RNFLT significantly	16.39 +/- 2.45	No correlation	RNFL reduction correlated with PERG delayed P50 and N95 implicit times and with P50-N95 reduced amplitude thickness and volume. Significant correlation between MMSE score and macular total volume. No changes in VEP.
Iseri et al.	2006	TD-OCT	30	28	113.16 +/- 6.72	87.46 +/- 23.78	All sectors decreased RNFLT significantly EXCEPT the temporal quadrant	18.5 +/- 6.3	No correlation	Decreased macular thickness and volume. Significant correlation between MMSE score and macular total volume. No changes in VEP.
Berisha et al.	2007	TD-OCT	8	9	93.8 +/- 10.4	85.5 +/- 7.4	Only superior quadrant affected significantly	23.8 +/- 5.1	Possible relation	Marked narrowing of the retinal venous blood column diameter and a reduction in retinal blood flow rate using laser Doppler
Paquet et al.	2007	TD-OCT	15	14	102.2 +/- 1.8	76.6-89.2	All four quadrants seemed to be affected significantly	16.6-22.6	No correlation	Study also involved MCI group
Y. Lu et al.	2010	TD-OCT	22	22	Shown in a double-peak manner that the RNFLT curve in AD patients lost the double-peak character and reduced average RNFLT		Only superior and inferior quadrants reached statistical significance	-	-	Variable fundus photograph abnormalities, including diffuse and wedge-shaped nerve fiber layer drop-out. Increased cup-todis
Kesler et al.	2011	TD-OCT	38	52	94.3 +/- 11.3	84.7 +/- 10.6	Only superior and inferior quadrant thinning reached statistical significance	23.6 +/- 4.3	No correlation	Study also involved MCI group
Moschos et al.	2012	SD-OCT Stratus OCT	30	30	Shown only RNFLT thickness in each quadrant		All sectors decreased peripapillary RNFLT significantly	-	-	Central macular thickness was significantly lower in AD patients. Also showed changes of electrical activity in foveal and perifoveal regions using mERG.
Moreno-Ramos et al.	2013	SD-OCT Topcon 3D OCT-1000	10	10	108.8 +/- 2.2	94.5 +/- 2.2		16.4 +/- 1.5	Correlation	Also observed reduced RNFLT in Parkinson and Lewy body dementia
Marziani et al.	2013	SD-OCT Spectralis + RTVue-100	21	21	252.3 +/- 19.2 RTVue-100 283.8 +/- 21.7 Spectralis	244.1 +/- 17.9 RTVue-100 277.5 +/- 21.7 Spectralis	Peripapillary RNFLT diffusely decreased	15-26	-	Reduced macular RNFLT + GCL thickness
Kirbas et al.	2013	SD-OCT Spectralis	40	40	75 +/- 3.8	65 +/- 6.2	Selective (statistically significant) RNFLT	18-25	No correlation	-

Table 1 (continued)

First author	Year of publication	Technology	Sample size (number of eyes)		Average peripapillary RNFL thickness $\pm$ SD ( $\mu$ m)		Peripapillary RNFL quadrants most affected in AD patients	MMSE	Correlation between MMSE and RNFLT	Comments
			Controls	Patients with AD	Controls	AD patients				
Kromer et al.	2013 and 2014	SD-OCT Spectralis	42	42	Global difference AD versus control: -7.553		thinning in superior quadrant Nasal superior sector	22.59 $\pm$ 5.47	No correlation	Enlarged cup-to-disc ratio in AD, however not correlated with RNFLT. Also VEP showed no changes
Larrosa et al.	2014	SD-OCT Spectralis + Cirrus	61	151	98.2 $\pm$ 17.1 Cirrus 102.7 $\pm$ 6.7 Spectralis	97.5 $\pm$ 14.1 Cirrus 100.5 $\pm$ 13.0 Spectralis	Temporal quadrant most affected. All quadrants significantly affected <i>except</i> nasal quadrant.	18.31 $\pm$ 3.28	-	Retinal thinning significant in all areas except the fovea in AD patients
Ascascio et al.	2014	SD-OCT Stratus OCT	41	18	103.6 $\pm$ 8.9	64.7 $\pm$ 7- 15.2	All quadrants significantly affected <i>except</i> temporal quadrant	19.3 $\pm$ 7.8	Significant association between RNFLT and MMSE score	Study also involved MCI group. Macular thickness and volume reduced in AD patients
Garcia-Martin et al.	2014	SD-OCT Topcon 3D OCT-1000	28	20	89.2 $\pm$ 20.9	88.6 $\pm$ 20.5	Peripapillary RNFL thickness did not differ significantly between groups	Mild AD patients	-	Reduced macular RNFL thickness and macular volume in mild AD, the most sensitive areas being superior inner and temporal inner maculae
MP Bambo et al.	2014	SD-OCT Cirrus + Spectralis	57	57	Spectralis OCT 98.70 $\pm$ 10.1 Cirrus OCT 95.96 $\pm$ 9.5	Spectralis OCT 95.79 $\pm$ 10.7 Cirrus OCT 89.00 $\pm$ 10.2	Cirrus OCT: superior and inferior quadrants. Spectralis: inferior quadrants	-	-	Study showed chorioidal thinning in AD
Gharbiya et al.	2014	SD-OCT Spectralis	42	42	95.9 $\pm$ 8.5	96.8 $\pm$ 6.9	AD patients showed similar RNFLT compared with controls	22.2 $\pm$ 1.7	-	Study showed chorioidal thinning in AD
V Polo et al.	2014	SD-OCT Cirrus + Naxonal application of Spectralis	75	75	Spectralis OCT 99.61 Cirrus OCT 99.21	Spectralis OCT 98.50 Cirrus OCT 97.41	Significant thinning in the superior and inferior RNFL quadrants in AD patients. Also demonstrated retinal thinning in AD	15.9 $\pm$ 7.3	Correlation	This study evaluated reliability of OCT in Alzheimer's disease and suggests the Spectralis OCT is more reliable and more readily detects retinal pathologies than the Cirrus OCT.
Salobrar-Garcia et al.	2015	OCT Model 3D OCT-1000 Topcon	28	23	-	-	No statistically significant difference in peripapillary RNFL thickness in mild AD patients compared with controls	23.3 $\pm$ 3.1 (Mild AD)	-	Macular RNFL thickness was decreased in the fovea, inner quadrants, and outer temporal quadrant. Macular

Table 1 (continued)

First author	Year of publication	Technology	Sample size (number of eyes)		Average peripapillary RNFL thickness $\pm$ SD ( $\mu$ m)	Peripapillary RNFL quadrants most affected in AD patients	MMSE	Correlation between MMSE and RNFLT	Comments
			Controls	Patients with AD					
Cheung et al. (34)	2015	Cirrus HD-OCT using automatic segmentation	123	100	87.51 $\pm$ 2.00	85.89 $\pm$ 1.64	-	-	thinning occurs before RNFL thinning AD patients had reduced macular GC-IPL thicknesses in all sectors. MCI patients had reduced GC-IPL thickness. No differences in GC-IPL thickness between MCI and AD groups There were no significant RNFL changes between MCI and AD patient groups
E.O. Oktem et al.	2015	Zeiss CIRRUS HD 5000 model OCT (SD-OCT)	35	35	91.5 $\pm$ 7.1	80.6 $\pm$ 9.6	15.6 $\pm$ 5.0	Correlation	There were no significant RNFL changes between MCI and AD patient groups
Liu et al.	2015	Stratus OCT	39	63	100-12 $\pm$ 15.01	Mild AD patients: 91.61 $\pm$ 10.10 Moderate AD: 91.68 $\pm$ 12.37 Severe AD: 87.13 $\pm$ 17.05	-	Correlation	Thickness of superior quadrant RNFL gradually decreases with dementia progression from MCI to AD. There was also a reduction of RNFL in the inferior quadrant in patients with severe AD
L. Y. Gao et al.	2015	Zeiss Cirrus HD-OCT 4000	21	25	85.99 $\pm$ 1.90	98.60 $\pm$ 1.67	19.24 $\pm$ 0.64	No correlation	Macular volume significantly reduced in AD patients. Also compared patients with MCI vs AD

**Table 2** Studies of retinal fiber layer thickness (RNFLT) changes in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD), using OCT

First author	Year of publication	Technology	Sample size (Number of eyes)		Average peripapillary RNFLT thickness $\pm$ SD ( $\mu$ m)			Differences between MCI and AD	Correlation between MMSE and RNFLT	Comments
			Controls	MCI patients	AD patients	Controls	MCI patients			
Paquet et al.	2007	TD-OCT	15	23	26	102.2 $\pm$ 1.8	89.3 $\pm$ 2.7	76.6-89.2	No significant differences between MCI and AD	No correlation between MMSE and RNFLT
Kesler et al.	2011	TD-OCT	38	40	52	94.3 $\pm$ 11.3	85.8 $\pm$ 10.0	84.7 $\pm$ 10.6	No significant differences between MCI and AD	No correlation between MMSE and RNFLT
Ascaso et al.	2014	SD-OCT	41	21	18	103.57 $\pm$ 8.94	86.03 $\pm$ 7.26	64.75 $\pm$ 15.18	RNFL thickness in AD patients was significantly lower than in aMCI and controls in all quadrants <i>except</i> nasal quadrant	Correlation between MMSE and RNFLT in superior and nasal quadrants of AD patients, but not aMCI patient group
L. Y. Gao et al.	2015	SD-OCT	21	26	25	98.60 $\pm$ 1.67	92.38 $\pm$ 1.94	85.99 $\pm$ 1.90.	Overall, RNFLT of AD patients was less than that of MCI patients, with significant differences at inferior quadrant.	No correlation between MMSE and RNFLT
Liu et al.	2015	SD-OCT	39	26	63	100-12 $\pm$ 15.01	95.37 $\pm$ 17.11	Mild AD patients: 91.61 $\pm$ 10.10 Moderate AD: 91.68 $\pm$ 12.37. Severe AD: 87.13 $\pm$ 17.05	Selective superior quadrant RNFLT thinning in early AD. Inferior quadrant changes only significant in severe AD patients. Significant RNFLT difference between control group and MCI and AD, <i>EXCEPT</i> in nasal	Macular volume was slightly but significantly reduced in both MCI and AD patient groups when compared with controls, but no significant differences between aMCI and AD



Table 2 (continued)

First author	Year of publication	Technology	Sample size (Number of eyes)		Average peripapillary RNFL thickness $\pm$ SD ( $\mu$ m)			Differences between MCI and AD	Correlation between MMSE and RNFLT	Comments
			Controls	MCI patients	AD patients	Controls	MCI patients			
Oktem et al.	2015	SD-OCT	35	35	35	91.5 $\pm$ 7.1	82.5 $\pm$ 7.3	80.6 $\pm$ 9.6	Correlation between MMSE and RNFLT	
Cheung et al.	2015	SD-OCT using automatic segmentation	123	41	100	87.51 $\pm$ 2.00	87.00 $\pm$ 2.02	85.89 $\pm$ 1.64	No correlation between MMSE and RNFLT	AD patients showed significant reduction of GC-IPL thickness in all areas compared with controls. No statistically significant differences in GC-IPL thickness between AD and MCI

believed to reflect axonal loss, whereas macular volume reflects neuronal loss of RGC, since the neuronal bodies and dendrites are located in the ganglion cell/internal plexiform layer (GC-IPL), mostly in the macula lutea [50].

TD-OCT has been the most widely employed ocular imaging technique for assessment of optic nerve degeneration in AD [43–47], as well as for evaluating macular thinning in these patients [44].

Spectral-domain OCT (SD-OCT), a Fourier domain OCT technique, provided dramatically increased scanning speed and higher axial resolution when compared to TD-OCT technology, allowing the study of RGC and analysis of the GC-IPL layers [41, 49]. SD-OCT has been validated as a reliable technique for detecting subclinical RNFL and retinal atrophy in AD [64–66]. A number of studies using this technology have corroborated peripapillary RNFL thinning findings from TD-OCT studies. Figure 1 shows these changes in pRNFL thickness. In addition, one study using SD-OCT showed a diffuse reduction of the RNFL and GCL combined in AD [49], although the authors were not able to determinate which layer was most affected by AD. Later studies have demonstrated IPL thinning in AD patients [41, 50, 52, 56, 57]. This reduction of ganglion cell complex thickness (GC-IPL and RNFL layers) in AD occurs to a larger extent than that accounted for age-related GC-IPL loss alone (about 0.3  $\mu$ m/year) [54]. Macular GC-IPL thinning may be a more sensitive marker of earlier neurodegeneration in MCI and AD than evaluation of the retinal fibre layer. These findings are in agreement with the pathological findings of direct retinal involvement in dementia. Figure 2 illustrates the GC-IPL thinning as measured by SD-OCT.

Evidence from OCT studies also supports a role for TRD in disorders of the posterior visual pathway [34, 35, 67, 68] with visual field defects in these disorders correlating best with macular GCL thickness than with RNFL thickness [67, 68]. Likewise, OCT findings in AD suggest the contribution of TRD in the pathophysiology of visual changes. In addition to previous OCT studies showing reduced peripapillary RNFL thickness, a recent SD-OCT study found that reduced grey matter volumes of occipital and temporal lobes was independently associated with thinning of the GC-IPL and peripapillary RNFL in individuals without dementia [69]. Since those cortical regions are an early site of deposition of senile plaques and NFTs, the findings by Y.-T. Ong and co-workers raises the possibility that GC-IPL thinning may reflect neurodegenerative changes in the brain, even before the clinical onset of dementia.

Some questions remain to be answered before considering OCT a useful clinical biomarker for early detection of dementia and assessment of disease progression in AD. As stated earlier, peripapillary RNFL thinning has been demonstrated in a number of studies. However, differences have been reported regarding which retinal quadrants are

most affected. While some studies report preferential superior quadrant RNFL thinning in AD, which would explain the predominantly inferior visual field defects previously described in AD [40, 45, 47, 54, 70–72], other authors have reported different findings; these results are presented in Table 1. A meta-analysis of TD-OCT studies in AD demonstrated that peripapillary RNFL thinning occurred in all retinal quadrants [73]. However, more recent SD-OCT studies have reported different findings, with most SD-OCT studies suggesting selective superior RNFL thinning [39, 54, 70]. Two more recent meta-analyses, which used both TD-OCT and SD-OCT studies, aimed to determine the diagnostic utility of OCT measurements of RNFL thickness in AD [74, 75]. While confirming significant peripapillary RNFL thinning in AD, these meta-analyses reached different conclusions regarding which quadrants are most affected. Whether or not a correlation exists between retinal changes and severity of dementia also remains a controversial issue. While most OCT studies did not show correlation between Minimal Mental State Examination (MMSE) and peripapillary RNFL thinning (Table 2), one TD-OCT study reported correlation between MMSE scores and macular volume [44], and more recent studies using SD-OCT have indeed reported a significant correlation between MMSE scores and RNFL thickness [50, 66, 72, 76, 77]. Studies comparing changes in RNFLT in MCI and AD (Table 2) have also yielded conflicting results, although the majority reported no statistically significant differences between MCI and AD patient groups [46, 47, 54, 77]. The meta-analyses by K.L. Thomson et al. and G. Coppola et al. [74, 75] also tried to determine the utility of OCT as a tool for evaluating disease progression, and prognostic significance of GC-IPL and RNFL thickness in MCI and AD. Both meta-analyses concluded that OCT can be used to detect early abnormalities in MCI, but their conclusions regarding which retinal quadrants are affected in MCI were conflicting—one concluded that MCI patients have selective superior quadrant RNFL thinning [74], while the other concluded that all quadrants but the superior one were affected [75]. In addition, they failed to determine

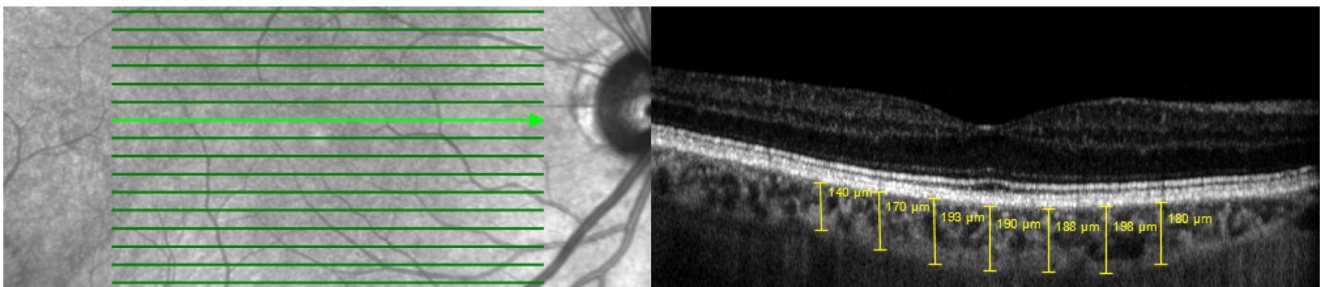
a correlation between RNFL and clinical severity of dementia [74].

Spectral-domain OCT (SD-OCT) using enhanced depth imaging modality (EDI) is a technology that allows visualization of the deeper structures of the eye such as the choroid. Choroidal thickness (CT) varies topographically within the posterior pole, being thickest under the fovea and thinnest in the nasal area. EDI-OCT has been validated as a reproducible modality for subfoveal CT measurements [60]. In addition, EDI-OCT findings have confirmed that CT significantly decreases with older age.

Choroidal thickness (CT) has been shown to be reduced in all regions in patients with AD, as measured by EDI-OCT Spectralis Heidelberg [61]. Figure 3 depicts these changes in choroidal thickness. These findings have been corroborated by further studies [62, 63]. One study also included patients with MCI, and observed reduced CT in this group, although no statistically significant differences between the MCI and AD patient groups were found [63]. Although CT is reduced, it remains to be elucidated whether or not choroidal thinning is correlated with MMSE scores, as authors report conflicting results. The results of these studies are shown in Table 3.

Swept source-OCT (SS-OCT) is another Fourier domain OCT technology. It has also an improved signal-to-noise ratio as compared to TD-OCT, providing higher image resolution. SS-OCT additionally offers some advantages over SD-OCT, including higher detection efficiency, increased sensitivity with image depth, reduced fringe washout and longer imaging range, higher penetration into the ONH and choroid, and lowered sensitivity to ocular opacities [41].

Ultrahigh-speed OCT based on swept laser technology enables rapid 3D imaging of the retina and Doppler OCT examination of ocular circulation with a non-invasive ocular angiography by optical coherence tomography. This can be a powerful methodology for measuring total retinal blood flow, which might be beneficial for assessing pathologic changes in diseases with impaired circulation of retina and choroid such as AD [78].



**Fig. 3** Choroidal thickness (CT) as measured by EDI-OCT (Spectralis Heidelberg)

**Table 3** Studies assessing choroidal thickness (CT) in patients with AD and in patients with MCI, as measured by EDI-OCT imaging modality

First author	Year of publication	Technology	Sample size (Number of eyes)			Subfoveal choroidal thickness ( $\mu\text{m}$ )			Central temporal choroidal thickness ( $\mu\text{m}$ )		
			Controls	MCI	Alzheimer patients	Controls	MCI	Alzheimer patients	Controls	MCI	Alzheimer patients
Gharbiya et al.	2014	Spectralis EDI-OCT	42	—	42	266.1 $\pm$ 93.5	—	200.9 $\pm$ 70.7	256.9 $\pm$ 80.5	—	—
Bayhan et al.	2015	RTVue-100 EDI-OCT	30	—	31	251.96 $\pm$ 48.03	—	221.48 $\pm$ 40.33	215.26 $\pm$ 49.63	—	—
Mehmet Bulut et al.	2015	Cirrus HD-OCT (EDI-OCT)	88	76	82	272.7 $\pm$ 60.1	228.7 $\pm$ 25.9	215.6 $\pm$ 64.5	250.2 $\pm$ 55.3	211 $\pm$ 49.9	—
First author	Central temporal choroidal thickness ( $\mu\text{m}$ )	Central nasal choroidal thickness ( $\mu\text{m}$ )	Central superior choroidal thickness ( $\mu\text{m}$ )	Central inferior choroidal thickness ( $\mu\text{m}$ )	Central inferior choroidal thickness ( $\mu\text{m}$ )	Central inferior choroidal thickness ( $\mu\text{m}$ )	Central inferior choroidal thickness ( $\mu\text{m}$ )	Central inferior choroidal thickness ( $\mu\text{m}$ )	Central inferior choroidal thickness ( $\mu\text{m}$ )	Central inferior choroidal thickness ( $\mu\text{m}$ )	Central inferior choroidal thickness ( $\mu\text{m}$ )
Alzheimer patients	Controls	MCI	Alzheimer patients	Controls	Alzheimer patients	Controls	Alzheimer patients	Controls	Alzheimer patients	Controls	Alzheimer patients
Gharbiya et al.	203.9 $\pm$ 73.9	249.7 $\pm$ 93.5	190.5 $\pm$ 67.5	263.6 $\pm$ 89.4	208.4 $\pm$ 68.7	245.3 $\pm$ 87.1	198.0 $\pm$ 71.6	—	—	—	—
Bayhan et al.	189.25 $\pm$ 30.22	213.96 $\pm$ 48.18	185.09 $\pm$ 39.02	240.86 $\pm$ 46.57	211.29 $\pm$ 43.01	234.30 $\pm$ 45.62	195.25 $\pm$ 38.91	—	—	—	—
Mehmet Bulut et al.	200.4 $\pm$ 60	244.2 $\pm$ 60.5	204.7 $\pm$ 53.6	194.9 $\pm$ 63.4	—	—	—	—	—	—	—

All areas were thinner in AD patients, except measurements 3.0 mm temporal to the fovea

All areas showed statistically significant choroidal thinning in both AD and MCI

## Conclusions

Patients with signs and symptoms of dementia undergo neuropsychological evaluation, and several clinical tools have been validated for that purpose, including the Clinical Dementia Rating (CDR) and Alzheimer's Disease Assessment Scale (ADAS). Diagnostic criteria can be used for clinical diagnosis of Alzheimer's disease, namely the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [68] and the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria. However, to date, the definitive diagnosis of AD can still only be made on pathologic examination. However, a number of diagnostic exams have been considered to be supportive of the clinical diagnosis. Neuroimaging technologies, namely computerized tomography (CT) scanning or magnetic resonance imaging (MRI) have shown medial temporal lobe atrophy. Reduced brain activity has been detected by changes in glucose metabolism in positron emission tomography (FDG-PET). Biochemical cerebrospinal fluid (CSF) markers have been suggested as potential biomarkers for early detection of Alzheimer's disease (decreased levels of CSF  $A\beta_{42}$  protein and increased CSF levels of tau and phosphorylated tau proteins) [79, 80].

Cicero (106–43 BC) stated “the face is a picture of mind as the eyes are its interpreter”; Matthew reveals in the Bible “the eye is the lamp of the body”, and it is attributed to Shakespeare the quote “the eyes are the window to the soul”.

Optical coherence tomography findings in many neurodegenerative diseases have revived this notion of the eye as the “window to the brain”. Anatomically and embryologically, the retina is known as an extension of the central nervous system; the fibers of retinal ganglion cell axons forming the optic nerve are the axons of the CNS and the retinal and cerebral vasculature share similar anatomic, physiological, and embryological characteristics.

OCT studies have provided useful information regarding retinal and choroidal changes in the eyes of patients with AD, as OCT findings are consistent with the findings from pathology studies of both human and animal models of AD. In addition, retinal changes in microvasculature may reflect microvascular disease in the brain.

These findings may render OCT a useful clinical tool for diagnostic and prognostic evaluation of MCI and AD patients. Newer, more sensitive imaging modalities for measurements of retinal layers and choroidal thickness will allow further understanding of the earliest changes in the retina of these patients. It is likely that macular inner retinal layers (GC-IPL and macular RNFL) neurodegenerative changes are the earliest events, followed by peripapillary RNFL thinning, but vascular changes both in choroid and in retina may also play a role in the initiation of the neurodegenerative processes. Further OCT studies

are thus needed to determine the progression of these neurovascular degenerative changes in MCI and AD.

## Literature research

We searched the PubMed and Google Scholar databases to identify articles published up to 27th March 2016, using the following key terms: “Alzheimer's disease”, “dementia”, “optical coherence tomography”, “visual function abnormalities”. In addition, we manually searched the reference lists of most primary articles and reviewed articles.

## Compliance with ethical standards

**Funding** No funding was received for this research.

**Conflicts of interest** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study, and for this type of study, formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

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