

## Retinal Imaging

# Retinal thickness correlates with parietal cortical atrophy in early-onset Alzheimer's disease and controls

Jurre den Haan<sup>a,\*</sup>, Sarah F. Janssen<sup>b</sup>, Jacoba A. van de Kreeke<sup>b</sup>, Philip Scheltens<sup>a</sup>, Frank D. Verbraak<sup>b,c</sup>, Femke H. Bouwman<sup>a</sup>

<sup>a</sup>Department of Neurology, Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands

<sup>b</sup>Ophthalmology Department, VU University Medical Center, Amsterdam, The Netherlands

<sup>c</sup>Ophthalmology Department, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

### Abstract

**Introduction:** The retina may reflect Alzheimer's disease (AD) neuropathological changes and is easily visualized with optical coherence tomography (OCT). Retinal thickness decrease has been correlated to AD, however, without information on amyloid status. We correlated retinal (layer) thickness to AD biomarkers in amyloid-positive early-onset AD (EOAD) patients and amyloid-negative controls.

**Methods:** We measured macular thickness and peripapillary retinal nerve fiber layer thickness with OCT in 15 EOAD patients and 15 controls and correlated retinal thickness to visual rating scores for atrophy on magnetic resonance imaging.

**Results:** Total macular thickness correlated to parietal cortical atrophy in both groups (Spearman  $\rho = -0.603$ ,  $P = .001$ ). Macular and peripapillary retinal nerve fiber layer thicknesses were not significantly decreased in EOAD compared to controls.

**Discussion:** Retinal thickness does not discriminate EOAD from controls but is correlated to parietal cortical atrophy in both groups. These findings may suggest reflection of cerebral cortical changes in the retina, independent of amyloid.

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### Keywords:

Optical coherence tomography (OCT); Retinal thickness; Biomarker; Alzheimer's disease; Retina; Cortical atrophy

## 1. Introduction

With the currently increasing amount of clinical trials for Alzheimer's disease (AD) and its prodromal stage, a patient-friendly and sensitive diagnostic method for an early diagnosis is urgently needed. The retina is embryologically derived from the neural tube, and as a protrusion from the brain, it shares many similarities with brain tissue. Through the pupil, the retina and its neurons are easily examined with optical coherence tomography (OCT) thus serving as a potential noninvasive diagnostic target in neurodegenerative

diseases such as AD, Parkinson's disease (PD), and dementia with Lewy bodies [1–4].

Currently, cortical atrophy on magnetic resonance imaging (MRI), as a biomarker for neurodegeneration, can be assessed with visual rating scores for global cortical atrophy, medial temporal lobe atrophy, and parietal cortical atrophy [5–7]. Typically, late-onset Alzheimer's disease (LOAD) shows medial temporal lobe atrophy, whereas early-onset Alzheimer's disease (EOAD) shows a diffuse pattern including parietal cortical atrophy [8]. Retinal thickness decrease measured with OCT might serve as a noninvasive proxy of cortical atrophy on MRI. Previous research showed both total macular and peripapillary retinal nerve fiber layer (RNFL) thinning in AD measured with OCT; however, this was not consistent in all studies. In a recent meta-analysis,

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\*Corresponding author. Tel.: +31204440685; Fax: +31204448529.

E-mail address: [j.denhaan1@vumc.nl](mailto:j.denhaan1@vumc.nl)

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we found an absolute decrease of peripapillary RNFL of 10  $\mu\text{m}$  and of total macular thickness of 16  $\mu\text{m}$  in AD compared to controls [9].

Similar to AD, glaucoma is a complex neurodegenerative disease and shows considerable overlap of neuroretinal changes with AD [10–14]. Previous studies did not account for the possible confounding effect of glaucoma on OCT measurements in AD patients, nor did they include established AD biomarkers as part of AD clinical diagnosis (NIA-AA) [10,11,15].

The objective of this study was to assess retinal layer thickness in amyloid-positive early-onset AD patients compared to amyloid-negative healthy controls, with the exclusion of glaucoma. In addition, correlation of retinal measures with established biomarkers in AD, such as cortical atrophy on MRI, was assessed.

## 2. Methods

### 2.1. Subjects

Fifteen subjects with EOAD and 17 controls (age < 70 years, Mini-Mental State Examination  $\geq 17$ , thus capable of giving informed consent) were included from the screening program of the Alzheimer Center of the VU University Medical Center embodying the basis of the Alzheimer Dementia Cohort (ADC) [16]. Controls comprised subjects with subjective cognitive decline, defined as subjective cognitive complaints without objective cognitive impairment on neuropsychological assessment, no signs of neurodegeneration on neuroimaging, and absence of amyloid pathology based on cerebrospinal fluid (CSF) and/or amyloid positron emission tomography (PET). Patients and controls underwent a standardized ADC screening program including MMSE, MRI, and lumbar puncture for amyloid- $\beta_{(1-42)}$ , tau<sub>181</sub>, and phosphorylated tau (pTau) levels. MRI visual rating scores for cortical atrophy were used for medial temporal lobe atrophy (MTA), global cortical atrophy (GCA), and parietal cortical atrophy (PCA) [6,7]. MRI scans were scored by a blinded rater before a multidisciplinary consensus meeting where a clinical diagnosis was made by consensus. All AD patients fulfilled NIA-AA criteria and had evidence of amyloid pathology in CSF and/or amyloid PET (florbetaben  $n = 13$ , florbetapir  $n = 9$ ) [15]. CSF tau<sub>181</sub>/amyloid  $\beta_{(1-42)}$  ratio  $> 0.52$  was considered indicative for AD [17]. Parametric images of amyloid-PET scans were assessed by experienced raters and visually interpreted as amyloid positive or amyloid negative following FDA guidelines for florbetaben and florbetapir. Exclusion criteria were (ophthalmological) conditions interfering with OCT quality/retinal thickness: severe cataract, age-related macular degeneration, and glaucoma, and neurological or systemic chronic conditions known to interfere with retinal thickness (e.g., multiple sclerosis, PD, diabetes mellitus, rheumatoid arthritis, sarcoidosis, Crohn's disease, and colitis ulcerosa). In addition, we

excluded subjects with ischemic stroke and/or mild-to-severe white-matter hyperintensities on MRI, operationalized as a Fazekas score  $> 1$  [18].

### 2.2. Eye examinations

Subjects were included within a year after the ADC screening program and underwent the following eye examinations: best corrected visual acuity, intraocular pressure (IOP) using noncontact tonometry (if IOP  $> 20$  mm Hg, we used contact applanation tonometry), slit-lamp examination of the anterior and posterior segment and fundus photography (Topcon TRC 50DX type IA), Heidelberg Retinal Tomography (HRT) optic nerve head analysis, and Frequency Doubling Technology for visual fields. Tropicamide 0.5% was administered for pupil dilation to facilitate optimal ophthalmic examination.

We followed the fourth European Glaucoma Guideline criteria: glaucoma was diagnosed when two of the three following measurements were abnormal: ocular pressure ( $> 21$  mm Hg), structural glaucomatous changes (examined with HRT using the Moorfields Regression Analysis), and functional changes (examined with Frequency Doubling Technology) [19]. All examinations were interpreted by an ophthalmologist and resident in ophthalmology (F.D.V. and S.F.J.). This study was designed and conducted according to the Declaration of Helsinki, and the study protocol was approved by the Ethical Committee of the VU University Medical Center. All patients gave their written informed consent in the presence of their caregiver.

### 2.3. Optical coherence tomography

Two protocols for both eyes were performed in each subject with Heidelberg Spectralis Spectral-Domain OCT: (1) central retina (macula) dense horizontal scanning; central  $20^\circ \times 20^\circ$  area; 49 B-scans (averaging 16 frames per B-scan); 512 A-scans per B-scan and (2) axonal ring scan around the optic nerve head for RNFL.

Peripapillary RNFL was measured in six sectors provided by Heidelberg software. Macular thickness was measured in the Early Treatment of Diabetic Retinopathy Study (ETDRS) map (fovea [ $\varnothing$  1 mm], and the mean of four quadrants of both the inner ring [ $\varnothing$  3 mm], area 2 to 5, and the outer ring [ $\varnothing$  6 mm], area 6 to 9) (Fig. 1). In the fovea, the inner and the outer ring segmentation analysis was performed with Heidelberg segmentation software (version 1.9.204.0) to calculate thickness of the following retinal layers: RNFL, ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, and retinal pigment epithelium (Fig. 1).

### 2.4. Statistical analysis

#### 2.4.1. Sample size calculation

In our previous meta-analysis with 887 AD patients and 864 controls, we found a mean RNFL difference of 10  $\mu\text{m}$

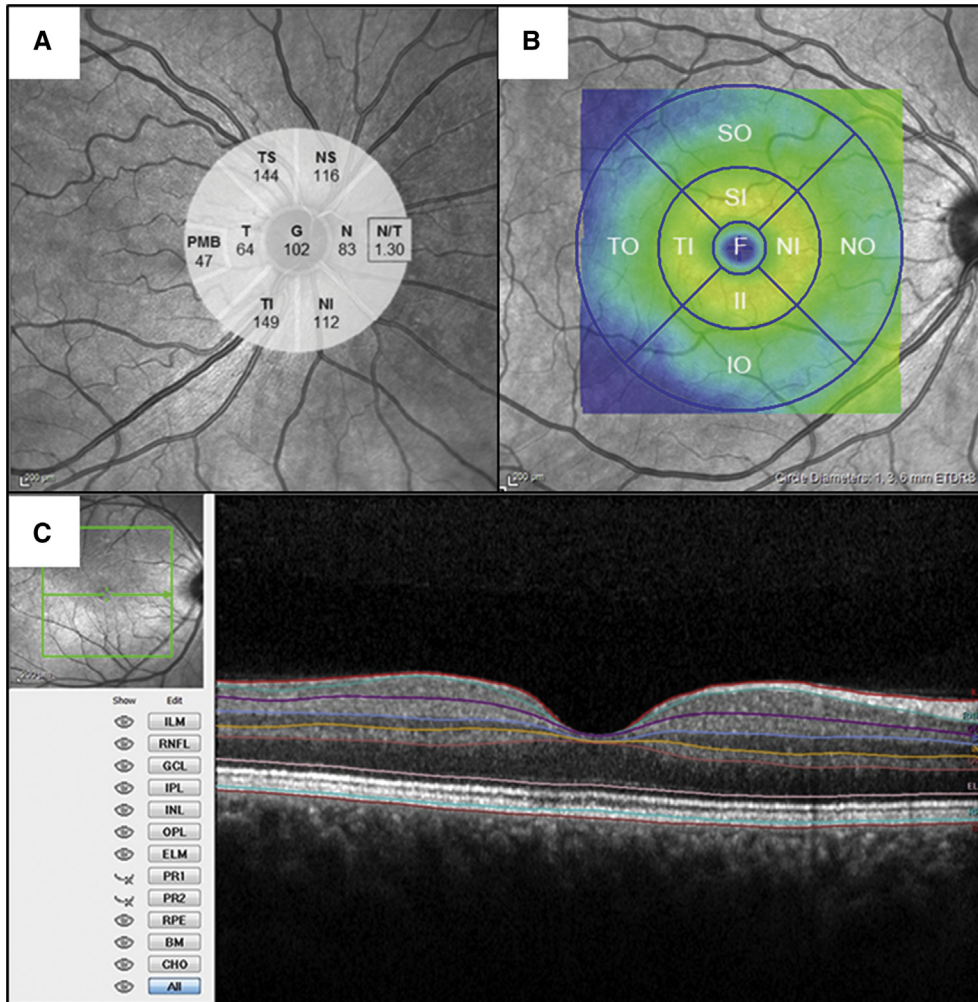


Fig. 1. Optical coherence tomography (OCT) images. (A) Around the optic nerve head (peripapillary): retinal nerve fiber layer (RNFL) thickness is measured in the following sectors: temporal superior (TS), nasal superior (NS), nasal (N), nasal inferior (NI), temporal inferior (TI), temporal (T). Mean RNFL thickness (G), nasal/temporal ratio (N/T), and papillomacular bundle (PMB) are also calculated. (B) In the macula, retinal thickness is measured in the fovea (F) (Ø 1 mm), inner ring (Ø 3 mm), and outer ring (Ø 6 mm) following the ETDRS grid. The inner ring and outer ring are subdivided into four sectors (superior, nasal, inferior, and temporal). (C) OCT scan (horizontal B-scan) through the macula shows segmentation of individual retinal layers: RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; and RPE, retinal pigment epithelium. Displayed are also ILM, inner limiting membrane; ELM, external limiting membrane; and BM, basal membrane.

with a standard deviation of 9 µm [9]. If the true effect is 10 µm with a standard deviation of 9 µm, 13 subjects in each group are needed to reject the null hypothesis of no difference between the AD and control group with a power of 0.80. We therefore included 15 subjects in each group.

#### 2.4.2. Data analysis

Means of retinal layer thickness in both eyes and visual cortical atrophy scores in both hemispheres were calculated. Data were (visually) tested for a normal distribution using histograms and Q-Q plots. We tested measures that were normally distributed with an independent-sample t-test, nonnormally distributed measures with a Mann-Whitney *U* test, and binary variables with a Fisher exact test. We used Pearson to correlate retinal layer thickness with CSF and MMSE and Spearman's  $\rho$  to correlate with MRI visual rating scores.

We considered but did not choose to correct with a post hoc Bonferroni correction for multiple testing because of the explorative nature of the study. Data analysis was performed with IBM SPSS Statistics (version 22.0), and Graph-Pad Prism (version 6.0) was used for graphs.

### 3. Results

#### 3.1. Baseline characteristics

Characteristics of patients and controls are listed in Table 1. We found no differences for sex, age, BCVA, and IOP. MMSE, atrophy scores on MRI, CSF levels for amyloid  $\beta_{1-42}$ , tau<sub>181</sub>, and pTau, and amyloid PET were indicative for an AD diagnosis in patients and were normal in controls. Two controls were excluded because of

Table 1  
Cohort characteristics

Variables	EOAD	Controls	P-value
<b>Demographics</b>			
Number	15	15	
Sex (m/f)	8/7	8/7	1.000*
Age	62.20 ( $\pm 3.67$ )	62.00 ( $\pm 6.27$ )	.916 <sup>†</sup>
MMSE	21.10 ( $\pm 3.49$ )	28.53 ( $\pm 1.68$ )	.000 <sup>‡</sup>
<b>CSF<sup>‡</sup></b>			
Amyloid <sub>1-42</sub>	527.21 ( $\pm 110.18$ )	1095.27 ( $\pm 143.17$ )	.000 <sup>‡</sup>
Tau <sub>181</sub>	739.21 ( $\pm 397.64$ )	220.27 ( $\pm 81.35$ )	.000 <sup>‡</sup>
pTau	104.57 ( $\pm 72.78$ )	37.45 ( $\pm 10.92$ )	.006 <sup>‡</sup>
<b>PET<sup>§</sup></b>			
Amyloid PET ( <i>n</i> positive/ <i>n</i> total)	7/7	0/13	.000*
<b>MRI</b>			
MTA	1.5 (0, 2.5)	0 (0, 2.0)	.003 <sup>  </sup>
GCA	1.0 (0, 2.0)	0 (0)	.001 <sup>  </sup>
PCA	1.5 (0, 2.0)	0 (0, 1.0)	.002 <sup>  </sup>
<b>Ophthalmologic</b>			
IOP (mm Hg)	15.97 ( $\pm 2.65$ )	15.83 ( $\pm 2.79$ )	.894 <sup>†</sup>
Visual acuity (logmar)	-0.04 ( $\pm .06$ )	-0.04 ( $\pm 0.11$ )	.919 <sup>†</sup>
HRT: Moorfield	1.43 (0.95, 2.13)	1.51 (1.14, 1.89)	0.106 <sup>  </sup>
FDT: MD	-1.86 (-20.99, 4.39)	0.15 (-3.82, 5.74)	<b>0.021<sup>  </sup></b>
FDT: PSD	5.05 (2.12, 14.64)	3.99 (2.74, 6.09)	0.202 <sup>  </sup>

Abbreviations: AD, Alzheimer's disease; m, male; f, female; MMSE, Mini-Mental State Examination; CSF, cerebrospinal fluid; pTau, phosphorylated tau; MTA, medial temporal lobe atrophy; GCA, global cortical atrophy; PCA, parietal cortical atrophy; IOP, intraocular pressure; HRT, Heidelberg Retinal Tomography; FDT, frequency doubling technology; MD, mean defect; PSD, pattern standard deviation; SCD, subjective cognitive decline.

NOTE. For normal distributed measures, means and standard deviations are shown. For nonnormal distributed measures, median, minimum, and maximum are shown. MMSE, CSF biomarkers, amyloid-PET, and visual rating scores for atrophy (in bold) significantly differed between EOAD and controls as expected. In addition an increased mean defect on visual field testing was observed in EOAD patients.

\*Fisher exact test.

<sup>†</sup>Independent-sample t-test.

<sup>‡</sup>CSF was missing in one AD patient and four controls.

<sup>§</sup>Amyloid PET was performed in 7 AD patients and 13 SCD subjects.

<sup>||</sup>Mann-Whitney *U* test.

epiretinal membrane in one and glaucoma in the other. None of the other participants fulfilled criteria for glaucoma. Two patients and two controls however could be considered glaucoma suspect due to suspicious but not abnormal optic nerve head topography and subtle visual field defects. Excluding these participants did not alter the results.

### 3.2. Retinal (layer) thickness

Peripapillary RNFL (AD 95.9  $\mu\text{m}$  [ $\pm 9.0$ ], HC 97.5  $\mu\text{m}$  [ $\pm 6.96$ ],  $P = .479$ ) and total retinal layer thicknesses in the ETDRS-defined areas (AD 316.1  $\mu\text{m}$  [ $\pm 11.0$ ], HC 320.5  $\mu\text{m}$  [ $\pm 7.5$ ],  $P = .136$ ) were not significantly different between groups (Fig. 2, Table 2). Segmentation of the ETDRS-defined foveal, inner, and outer ring areas showed no significant decrease of the individual retinal layers: RNFL, ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, and retinal pigment epithelium in AD patients (Table 2).

### 3.3. Correlation with AD biomarkers

We found a correlation between mean total macular thickness in the inner ring and outer ring with PCA (Spear-

man's  $\rho = -0.603$ ,  $P = .001$ ) and GCA (Spearman's  $\rho = -0.443$ ,  $P = .018$ ) on MRI in the total group, but not with MTA (Fig. 3). Correlations with PCA in separate diagnostic groups were comparable (AD: Spearman  $\rho = -0.561$ ,  $P = .029$ , controls: Spearman  $\rho = -0.587$

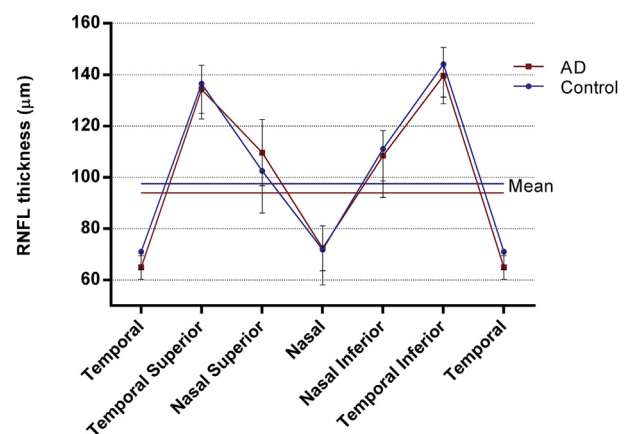


Fig. 2. Peripapillary RNFL (in  $\mu\text{m}$ ). Peripapillary retinal nerve fiber layer thickness (RNFL) presented as mean and in six sectors do not significantly differ between AD and controls. Abbreviation: AD, Alzheimer's disease.



Table 2  
Macular thickness: segmentation analysis

Retinal measure	AD	Controls	P value*
<b>Retinal thickness</b>			
Fovea	280.47 (18.00)	281.867 (17.19)	.853
Inner ring	339.63 (11.33)	343.69 (9.00)	.286
Outer ring	292.67 (11.46)	297.30 (8.34)	.216
<b>RNFL</b>			
Fovea	12.70 (2.07)	13.17 (1.68)	.503
Inner ring	21.92 (1.91)	21.81 (1.73)	.872
Outer ring	34.17 (3.33)	35.57 (3.92)	.303
<b>GCL</b>			
Fovea	15.47 (3.90)	15.67 (3.36)	.881
Inner ring	50.73 (2.99)	51.26 (2.83)	.620
Outer ring	34.47 (2.16)	35.05 (2.02)	.456
<b>IPL</b>			
Fovea	21.67 (3.72)	22.00 (3.39)	.799
Inner ring	41.55 (1.90)	41.88 (2.05)	.648
Outer ring	28.57 (1.62)	28.94 (1.47)	.512
<b>INL</b>			
Fovea	22.33 (5.74)	21.57 (3.57)	.664
Inner ring	41.18 (2.87)	40.91 (2.63)	.786
Outer ring	32.47 (1.62)	32.54 (1.56)	.902
<b>OPL</b>			
Fovea	26.93 (4.66)	25.87 (3.40)	.480
Inner ring	32.39 (4.30)	33.49 (3.30)	.439
Outer ring	27.28 (1.97)	27.78 (2.23)	.515
<b>ONL</b>			
Fovea	94.97 (11.05)	97.13 (8.48)	.552
Inner ring	70.21 (8.66)	72.71 (6.78)	.386
Outer ring	56.54 (6.81)	58.68 (5.92)	.367
<b>RPE</b>			
Fovea	16.50 (1.31)	16.30 (1.10)	.654
Inner ring	15.18 (0.60)	15.58 (1.39)	.323
Outer ring	13.50 (0.70)	13.78 (1.30)	.476
Macular volume (mm <sup>3</sup> )	8.51 (0.40)	8.69 (0.21)	.146

Abbreviations: RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; RPE, retinal pigment epithelium.

NOTE. Retinal thickness in  $\mu\text{m}$  (SD) in the macula of all individual layers and macular volume do not significantly differ between AD and controls.

\*Independent-sample t-test.

$P = .035$ ). The correlation with GCA in the AD subgroup was significant (Spearman  $\rho = -0.592$ ,  $P = .020$ ). All controls were scored GCA 0, and as a result, no correlation could be calculated. Total macular thickness in the fovea, the inner ring, and the outer ring were not correlated with CSF amyloid  $\beta_{1-42}$ , tau<sub>181</sub>, and p-tau levels. Mean RNFL was not correlated with CSF amyloid  $\beta_{1-42}$ , tau<sub>181</sub>, and p-tau levels or any of the cortical atrophy scores on MRI. No correlation with MMSE as measure for disease severity was found.

#### 4. Discussion

We showed that total macular thickness does not differ between AD and controls but does correlate with posterior cortical atrophy in both EOAD and controls, suggesting a relationship between the eye and brain that is independent of amyloid. The PCA visual rating score incorporates atro-

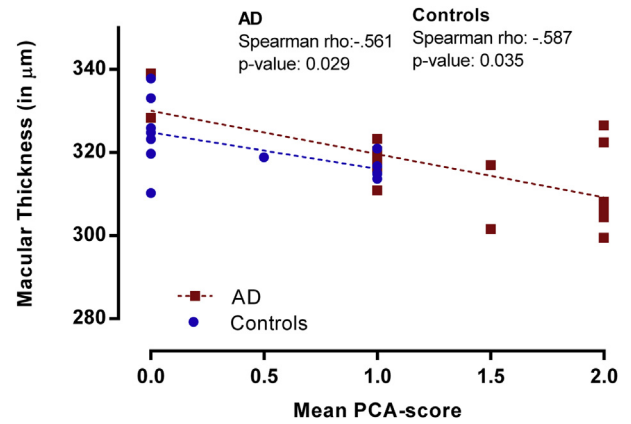


Fig. 3. Correlation between macular thickness and parietal cortical atrophy (PCA). Scatterplot visualizing the inverse correlation between macular thickness (mean of inner ring and outer ring of ETDRS grid) and mean visual rating score for parietal cortical atrophy on MRI. Abbreviation: AD, Alzheimer's disease; MRI, magnetic resonance imaging.

phy of the posterior cingulate, parietal-occipital sulcus (including the cuneus), and parietal lobe, covering cortices involved in optical processing [7]. Our findings suggest a direct correlation between macular thinning and focal neuronal loss of these cortical areas.

Only few studies described the relation between retinal layers and MRI features in cognitive impairment and/or controls. One study found an association between decreased brain gray-matter volume and disrupted white-matter microstructure and retinal layer thickness that was present only in controls and not in cognitively impaired patients [20]. Others described a relation between medial temporal lobe volume with RNFL thickness and total macular thickness in cognitively healthy [21]. This confirms the relation we found between retinal thinning and cortical atrophy. Remarkably, no study assessed this relationship specifically in a group of AD patients. We added to this literature in relating cortical atrophy measurements of AD patients to retinal thickness, also taking parietal cortical atrophy in account.

In contrast to previous studies, we did not find retinal thickness to be decreased in AD in this clearly defined and biomarker-proven cohort [3,9,22]. The absence of retinal thickness thinning in the current EOAD cohort, compared to previous studies with OCT in predominantly LOAD, may be a reflection of differences between EOAD and LOAD. Neuroradiologically, for example, MTA is often more prominent in LOAD compared to EOAD [8]. MTA is however also affected by age and should therefore be taken into account when assessing atrophy [8,23]. Like MTA, retinal thickness decreases with age, and therefore, retinal thinning may be more prominent in LOAD compared to EOAD [24,25] explaining the lack of RNFL thinning in this study.

On the other hand, EOAD often shows a diffuse pattern of posterior atrophy on MRI (posterior cingulate cortex, temporo-parietal areas, and precuneus), while hippocampal atrophy may be absent [26,27]. As these regions contain cortices involved in visual processing, retrograde atrophy of

the retina might be expected [28,29]. Despite the presence of posterior atrophy in our EOAD cohort, no decrease in retinal thickness was observed. Thus, contraintuitively, our data showed no support for retrograde atrophy resulting from atrophy in cortices involved in visual processing in EOAD.

One of the key strengths of this study is the use of amyloid biomarkers. To assess the retinal changes as a result of AD, without the contribution of age-related (neurodegenerative) factors, we deliberately designed this study in an EOAD cohort with confirmed amyloid pathology in CSF and/or amyloid PET. Previous studies with OCT in AD lacking amyloid biomarker confirmation might have included a heterogeneous patient cohort with different dementia types. Clinical amyloid-PET studies show that a clinical diagnosis of AD is not confirmed by amyloid PET in 5%–38% of the cases [30–33] and neuropathological research reported a mismatch of clinical and neuropathological diagnosis of at least 17% [34]. Other studies in neurodegenerative diseases showed that retinal thinning is also present in PD and dementia with Lewy bodies [1,4,35]. This stresses the need to use disease-specific biomarkers as part of inclusion criteria to assess cohorts based on their underlying neuropathology.

Another strength is the assessment of glaucoma. Because both AD and glaucoma are neurodegenerative diseases with progressive loss of the neuronal tissue and overlapping pathological molecular pathways, glaucoma should be considered as a possible confounder in the relationship between AD and retinal thickness [10–14]. We therefore strictly assessed glaucoma with both structural and functional tests and found that visual field defects were more often present in AD. This may be explained by the fact that visual field testing is not only a retinal but also a cognitive task and might thus be challenging for AD patients to perform. Nevertheless, none of the patients fulfilled clinical criteria for glaucoma, ruling it out as a cause of retinal thinning in both the EOAD and control groups.

Limitations of this study are its small number of patients and its cross-sectional design. The presented cohort is powered to detect a true effect of  $\geq 10 \mu\text{m}$  of mean RNFL thickness as reported in previous studies [9]. To detect a smaller true effect, a larger cohort is needed. Second, comparing retinal thickness decrease over time may be more sensitive for a neurodegenerative disease process, independent of amyloid load, and thus may be suitable as an alternative to MRI for showing progression over time.

Future studies should include more subjects including a LOAD group, longitudinal measurements, and disease-specific imaging aiming to detect retinal amyloid. Correlation with volumetric MRI data (e.g., hippocampus, optical tract, cortical thickness) may add to the understanding of the relation between retinal and cerebral neuronal loss.

## 5. Conclusion

In this amyloid-proven cohort without glaucoma, retinal layer thickness is correlated to parietal cortical atrophy in

both EOAD and controls. This suggests reflections of cortical thickness in the retina. Longitudinal studies including a larger number of EOAD and LOAD patients correlating retinal thickness with biomarkers for amyloid/neuronal injury as well as disease specific biomarkers (e.g., retinal amyloid) are needed to elucidate the possible role of the retina as a source of diagnostic and/or prognostic biomarkers in AD.

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## RESEARCH IN CONTEXT

1. Systematic review: Previous studies showed that retinal thinning is present in Alzheimer's disease and may be used as a noninvasive biomarker for neurodegeneration. However, no information on amyloid status to support a clinical Alzheimer's disease diagnosis was present in these studies.
2. Interpretation: Our study shows that retinal thickness does not discriminate amyloid positive early-onset Alzheimer's disease from amyloid negative controls but is correlated to parietal cortical atrophy in both groups. This finding may suggest reflection of cerebral cortical changes in the retina, independent of amyloid.
3. Future directions: Larger and longitudinal cohorts comparing retinal thickness with biomarkers for amyloid and neuronal injury are needed to elucidate the possible role of retinal thickness as a diagnostic and/or prognostic biomarker in (early-onset) Alzheimer's disease.

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