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Association of Brain Volume and Retinal Thickness in the Early Stages of Alzheimer's Disease

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Abstract

Background-—The eye has been considered a 'window to the brain,' and several neurological diseases including neurodegenerative conditions like Alzheimer's disease (AD) also show changes in the retina.

Objective-—To investigate retinal nerve fiber layer (RNFL) thickness and its association with brain volume via magnetic resonance imaging (MRI) in older adults with subjective or objective cognitive decline.

Method-—75 participants underwent ophthalmological and neurological evaluation including optical coherence tomography and MRI (28 cognitively normal subjects, 26 with subjective cognitive decline, 17 patients diagnosed with mild cognitive impairment, and 4 with AD). Differences in demographics, thickness of RNFL, and brain volume were assessed using ANCOVA, while partial Pearson correlations, covaried for age and sex, were used to compare thickness of the peripapillary RNFL with brain volumes, with $p<0.05$ considered statistically significant.

Results-—Mean RNFL thickness was significantly correlated with brain volumes, including global volume (right eye r=0.235 p=0.046, left eye r=0.244, p=0.037), temporal lobe (right eye r=0.242 p=0.039, left eye r=0.290, p=0.013), hippocampal (right eye r=0.320 p=0.005, left eye r=0.306, p=0.008), amygdala, (left eye r=0.332, p=0.004), and occipital lobe (right eye r=0.264 p=0.024) volumes.

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CONFLICT OF INTEREST

Professor Alon Harris would like to disclose that he received remuneration from Adom, Qlaris, and Luseed for serving as a consultant, and he serves on the board of Adom, Qlaris, and Phileas Pharma. Professor Harris holds an ownership interest in Adom, Luseed, Oxymap, Qlaris, Phileas Pharma, and QuLent. All relationships listed above are pursuant to Icahn School of Medicine's policy on outside activities.

Conclusion-—RNFL thickness in both eyes was positively associated with brain volumes in subjects with subjective and objective cognitive decline. The RNFL however did not correlate with the disease, but the small sample number makes it important to conduct larger studies. RNFL thickness may be a useful non-invasive and inexpensive tool for detection of brain neurodegeneration and may assist with diagnosis and monitoring of progression and treatment in AD.

Keywords

Neurodegeneration; Alzheimer's disease; Brain volume; Retinal nerve fiber layer; Optical coherence tomography; MRI

INTRODUCTION

Alzheimer's disease (AD) leading to dementia is one of the most common neurological disorders affecting older adults with approximately 5.4 million cases in United States (US). This number is expected to increase to 13.8 million in the US and to more than 115 million worldwide by 2050[1, 2]. The economic burden on society and family amounts to billions of dollars annually for health care, long term care, and hospice services[1]. Consequently, great emphasis is placed on studying the pathogenesis and techniques for early diagnosis and prompt treatment to prevent the devastating results of AD. In recent years, there has been significant progress in clinical research on the pathology, diagnosis, prevention, and treatment of AD.

Pathologically, AD is characterized by accumulation of extracellular amyloid-beta (Aβ) peptide plaques and hyperphosphorylated tau forming intracellular neurofibrillary tangles in the brain [3]. Aβ deposition in the brain takes place gradually over many years before the patient develops symptoms. Studies have also shown deposition of Aβ in the retina concurrent with the deposition in the brain [4–7]. With advances in neuroimaging techniques including MRI and PET scanning, it is now possible to map and quantify the Aβ deposits, which aids in identifying cases of preclinical AD before the development of symptoms characteristic of AD [8]. Treatment studies that target Aβ deposits in AD have been unsuccessful to date, perhaps because by the time a clinical diagnosis is made, neurodegeneration is already underway and is unlikely to be reversed [3]. Screening for AD using MRI or PET imaging techniques faces several challenges. Imaging techniques are expensive and time-consuming. Further, PET uses radioactive tracers to detect AD pathology, which precludes it from being used for population-based screening. Thus, there is an urgent need for less expensive and non-invasive methods to screen persons at risk for the development and progression of AD.

Neurodegeneration is one of the early pathological features of AD and may be present long before the clinical symptoms of AD become evident [9]. Most parts of the brain are susceptible to atrophy in AD, but the limbic system, temporal lobe, and the parieto-occipital cortices are predominantly affected [10–12]. Brain atrophy progresses at a much faster rate in AD patients compared to normal aging, as much as 10 times faster in susceptible areas like the hippocampus [13, 14]. Recent advances in MRI techniques help to identify and

quantify the thickness and volume of brain structures and play a significant role in studying disease progression and effects of treatment [15]. (Figure 1)

The eye has been termed the ”window to the brain,” and the retina is a part of the central nervous system, which originates in the developing diencephalon and forms a sensory extension of the brain containing a high density of neuronal cells and fibers [16]. The retinal nerve fiber layer (RNFL) forms the optic nerve, which directly connects the retina to the brain. Additionally, as a part of the central rather than peripheral nervous system, the optic nerve has several structural and functional similarities with the brain including the presence of neurons, glial cells, and a blood retinal barrier [17]. The retina, through the optically clear media of the eye, is easily accessible for visualization and can be segmented into individual layers measured using optical coherence tomography (OCT) with micrometer resolution [18]. Several studies have previously examined retinal thickness in AD and found that the retina becomes progressively thinner as AD progresses [19, 20]. (Figure 2)

In this study, we included cognitively normal subjects (CN), patients with subjective cognitive decline (SCD), mild cognitive impairment (MCI), and AD. We examined the association of brain volume with the RNFL thickness in the peripapillary retina and the macular thickness. This study focuses primarily on early-stage disease, whereas previous studies have often reported changes only in unimpaired individuals or in AD[21–23]. Ultimately, understanding the relationship between the brain and the retina, an extension of the brain, could assist in applying OCT for early detection and monitoring of progression of the disease. Thus, OCT measures could potentially be an inexpensive and less invasive method for the early detection of prodromal and/or clinical AD.

METHODS

Participants

This study utilizes data from the Indiana Alzheimer’s Disease Research Center (IADRC) Indiana Memory and Aging (IMAS) cohort (inclusion criteria age>50 years). Specifically, 75 participants including 28 CN, 26 SCD, 17 MCI, and 4 AD underwent a complete ophthalmological examination, OCT, neurological examination, cognitive and clinical testing, and MRI. SCD participants had subjective impairment of cognition as measured using the Cognitive Change Index (CCI) and no impairment on cognitive testing; MCI patients were functioning independently but had concerns about cognition from themselves, an informant, and/or a clinician and evidence of impaired cognitive testing (>−1.5 standard deviations) in one or more cognitive domains (most commonly memory); AD patients had an impaired ability to function independently at work or usual activities with evidence of impaired cognitive testing in one or more domains. Written informed consent was obtained from all participants and the study followed the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of Indiana University.

Exclusion criteria were primary open-angle glaucoma with elevated intraocular pressure (IOP), age-related macular degeneration, neurobehavioral risk factors including head injury, history of stroke, epilepsy, history of brain tumor, malignant or benign, migraine if frequent, severe, or interfering with functioning, multiple sclerosis or other demyelinating

disorder, non-Alzheimer's disease neurodegenerative disorder, mitochondrial disease, HIV/AIDS, brain aneurysm or arteriovenous malformation. Other exclusion criteria include medical conditions/history potentially affecting brain function or longevity relevant to participation and follow-up including: congestive heart failure, kidney failure with dialysis, liver failure, chronic obstructive pulmonary disease with oxygen dependence, other severe or medically uncontrolled conditions, any history of cancer treated with systemic chemotherapy, hormonal therapy (estrogen or androgen deprivation) or radiation therapy, treatment with chemotherapy or radiation therapy for another health condition, currently taking prescription medications or other substances that might influence neurochemistry, hemodynamic function, or cognitive performance. All included data excluded retinal diseases affecting the RNFL or macula and excluded any retinal distortion or image artifacts.

Ophthalmological examination

The ophthalmologic examination included best corrected visual acuity, IOP measurement, refraction, slit-lamp examination, indirect fundoscopy, fundus photography and OCT of the macula and optic disc. Pupil dilation was achieved using tropicamide 0.5% and phenylephrine 2.5%. OCT images and photographs were assessed by an experienced neuro-ophthalmologist for unexpected pathology (DDM). Participants suffering from ophthalmological conditions interfering with the retina or image quality were excluded prior to analyses (severe cataract, macular degeneration, primary open-angle or closed-angle glaucoma, diabetic retinopathy, vascular occlusions, and refractive error <−8 diopters or >+5 diopters).

Optical Coherence Tomography

HD-OCT images were obtained using Cirrus HD OCT software version 7.5 (Carl Zeiss) using a Cirrus 5000 machine (Carl Zeiss Meditech AG, Germany). OCT examinations were performed by the same operator who was experienced in acquiring OCT images. The Optic Nerve Head and RNFL analysis is done using the Optic Disc Cube 200 × 200 scanning protocol. Cirrus macular scan parameters were derived from the Early Treatment Diabetic Retinopathy Study (ETDRS) grid using central subfield retinal thickness with average thickness of the retina in a disc-shaped region of 1 mm centered on the fovea. All scans were reviewed for image quality and analysis artifacts.

MRI

MRI data was acquired using a single Siemens Prisma 3T scanner with a 64-channel RF receiver head coil. The participants underwent T1-weighted imaging using a 3-dimensional magnetization rapid gradient echo (MPRAGE) sequence with imaging parameters that matched the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI2) protocols. MPRAGE scans were processed using Freesurfer version 6 to generate measures of hippocampal and whole brain volume, as well as lobar volume estimates. Total white matter hyperintensities (WMHI) were determined using the Lesion Segmentation Tool (Lesion Growth Algorithm) implemented in SPM12.

Statistical Analysis

The statistical analysis was performed using IBM SPSS version 25. An analysis of variance (ANOVA) was performed to determine the relationship of diagnostic group with demographics, the thickness of the RNFL, and brain volumes. Multiple comparisons using Bonferroni's method was performed to examine the differences between the diagnostic groups in detail. Partial Pearson correlations, covaried for age and sex, were used to directly compare peripapillary RNFL thickness with WMHI, as well as volumes of the total brain, frontal, parietal, temporal, and occipital lobes, hippocampus, amygdala, and cingulate gyrus. Principal component analysis (PCA) was performed for the brain volume estimates and RNFL thickness estimates to reduce the dimension of the data and determine the number of independent regressions for the purpose of correcting for multiple comparisons. We also performed a subgroup analysis in the at-risk individuals (including only patients in the preclinical and MCI stage) and excluding the patients with AD to confirm that the associations were not being driven by the small dementia group.

RESULTS

The four study groups (CN, SCD, MCI, AD) were well-balanced for age, race/ethnicity, and IOP. Among the groups there was significant difference in memory (immediate and delayed recall), general cognition (MoCA Total Score), dementia severity (CDR-Sum of Boxes), and self- and informant-based complaints (all $p<0.001$; Table 1), with MCI and AD patients performing more poorly than CN and SCD, as expected.

Macular thickness and RNFL thickness in all four quadrants surrounding the optic nerve for each eye were compared among the study groups. Although there was a progressive thickening of the macula and thinning of the RNFL from cognitively normal to AD, no statistically significant difference was observed between the study groups in the thickness of the macula or the RNFL thickness in either eye (Table 2).

Average RNFL thickness was significantly correlated with brain volume estimates, including with global volume (right eye: $r=0.235$ $p=0.046$; left eye: $r=0.244$, $p=0.037$), temporal lobe (right eye: $r=0.242$, $p=0.039$; left eye: $r=0.290$, $p=0.013$), lateral temporal lobe (right eye: $r=0.249$, $p=0.034$; left eye: $r=0.298$, $p= 0.011$), cingulate cortex (right eye: $r=0.244$, $p=0.037$), and occipital lobe (right eye: $r=0.264$, $p=0.024$) (Figure 3; Table 3; all $p<0.05$).

The nasal RNFL thickness in the right eye was found to be significantly correlated with global volume ($r=0.276$, $p=0.018$), temporal lobe volume ($r=0.230$, $p=0.050$), lateral temporal lobe ($r=0.244$, $p=0.038$), occipital lobe volume ($r=0.279$, $p=0.017$), and frontal lobe volume ($r=0.242$, $p=0.039$). Parietal lobe volume was found to be significantly correlated with nasal RNFL thickness in both eyes (right eye: $r=0.300$, $p=0.010$, left eye: $r=0.236$, $p=0.044$). Other significant associations between brain volumes and RNFL quadrant thickness measures were observed and are detailed in Table 3 (all $p<0.05$).

PCA was performed and revealed that only two independent imaging and three independent OCT variables exist, thus bringing the total correlation tests to be six. Using this number as the Bonferroni correction makes the p-value cutoff meeting correction for multiple

comparisons to be 0.05/6 giving a corrected p-value of 0.008. After correction, associations between mean RNFL thickness in both eyes and hippocampal volume, as well as mean RNFL thickness in left eye and amygdala volume (Figure 4, Table 3) remained significant.

The subgroup analysis of at-risk participants (CN, SCD, MCI) showed that the positive correlation between RNFL thickness and brain volume was maintained, especially in the left eye. Mean RNFL thickness in left eye was significantly associated hippocampal (r=0.319, p=0.007), amygdala (r=0.350, p=0.003), and temporal lobe volumes, specifically in the lateral temporal lobe (temporal lobe: r=0.289 p=0.016; lateral temporal lobe: r=0.295, p=0.014), as was RNFL thickness in the superior quadrant of the left eye (temporal lobe: r=0.249, p=0.039; lateral temporal lobe: r=0.254 p=0.035). Additional associations can be found in Supplemental Table 1. As in the whole group analysis, only the association between left eye mean RNFL thickness and hippocampal and amygdala volumes was still significant after correction for multiple comparisons.

DISCUSSION

In this study, we observed that patients with cognitive decline show a positive association between RNFL thickness and brain volume. Specifically, regions of the limbic system, including hippocampus, amygdala, cingulate gyrus, and temporal lobe, showed significant correlations with the RNFL thickness. Additionally, the occipital, frontal, and parietal lobes and the global brain volume also showed a significant association with thickness of the RNFL. These findings were observed in the full sample, as well as in an at-risk only sample.

To the best of our knowledge, this is one of the first studies in patients with cognitive decline to demonstrate a positive association between brain volume and neurodegeneration seen in retina via measurement of peripapillary RNFL thickness across the clinical spectrum [34]. Further, all participants received a full ophthalmologic exam prior to inclusion, removing any effects of confounding ophthalmologic conditions associated with aging.

Our study involved patients at various stages of cognitive decline, including cognitively normal individuals without significant cognitive concerns, SCD participants, and patients diagnosed with cognitive impairment (MCI/AD). Several studies have evaluated the thickness of the peripapillary RNFL in patients with MCI and AD and have observed a thinning of the peripapillary RNFL in all four quadrants as the disease progresses [24, 25]. The relationship between retinal thickness and brain volume in cognitively normal subjects has been evaluated in several studies and they have identified thinning of the RNFL to be associated with a general reduction in gray-matter and white-matter volume [26]. The medial temporal lobe volume, hippocampal volume, and volume of the occipital or pericalcarine cortex have been found to be associated with thinning of RNFL in normal aging adults [27–29]. More detailed studies have proposed a quadrant-specific association with these regions of the brain that is vulnerable to neurodegeneration and thinning of the retina [23]. In nondemented elderly individuals, an association between hippocampal and cingulate gyrus atrophy and thinning of the RNFL was identified, [23, 30, 31] and the RNFL thinning was also found to be associated with episodic memory loss [30]. Shi et al. demonstrated an association between medial temporal lobe volume and temporal quadrant

RNFL thickness, and that the occipital lobe volume was associated with thinner RNFL in the inferior quadrant. Casaletto et al. demonstrated an association between medial temporal lobe volume and macular volumes [23, 27]. Mutlu et al. reported that lower gray matter density in the visual cortex is associated with thinner RNFL and higher mean diffusivity in the optic radiations [26].

Our study lends credence to the theory that retinal changes occur in tandem with brain pathology, and the retina may show signs of associated neurodegeneration [32]. The vascular changes and inflammation promote the accumulation of extracellular Aβ peptide in both the brain and retina and leads to synaptic and neuronal loss and death [33], which is manifested as thinning of the RNFL on OCT imaging.

Limitations

Our study has several limitations that might affect the interpretation of the results. First, the number patients in the AD group (n=4) are very low compared to the CN and SCD groups. Thus, our cohort is mostly composed of individuals who are normal or are in the very early stages of the disease. Consequently, our results may be skewed towards early findings in the disease spectrum. In addition, the sex distribution in the AD group does not mirror the known higher risk for AD in females. Future studies in larger studies are needed to directly examine sex-related effects on the retina in AD in a stratified manner. Second, we excluded all patients with open-angle glaucoma, a neurodegenerative disease that has been closely linked to AD, to avoid confounding of the results. Hence, we may have inadvertently missed a clinically significant relationship between retinal thinning and AD that is not confounded by but is mediated by open-angle glaucoma. Finally, we only evaluated these associations on a cross-sectional basis. Future longitudinal studies incorporating both imaging and OCT measures, especially in the early stages of disease, will provide important information about timing of the neurodegenerative changes in both the brain and retina.

CONCLUSION

The retina is an extension of the brain and as such, reflects the neurodegeneration seen within the brain in subjects with cognitive decline. Worldwide the burden of dementia and AD on healthcare and the economy is tremendous and will continue to increase necessitating the need for improved diagnostic and monitoring techniques. Brain imaging is the current gold standard diagnostic modality for AD patients, but this presents several challenges including high cost, exposure to radioactive isotopes, long duration of the procedure, and lack of accessibility. These challenges plague population-based screening and monitoring for AD onset and progression on a large scale. To overcome these obstacles, non-invasive retinal imaging applications such as OCT may be a useful tool for screening at-risk populations, monitoring progression of the disease, and evaluating the effects of AD treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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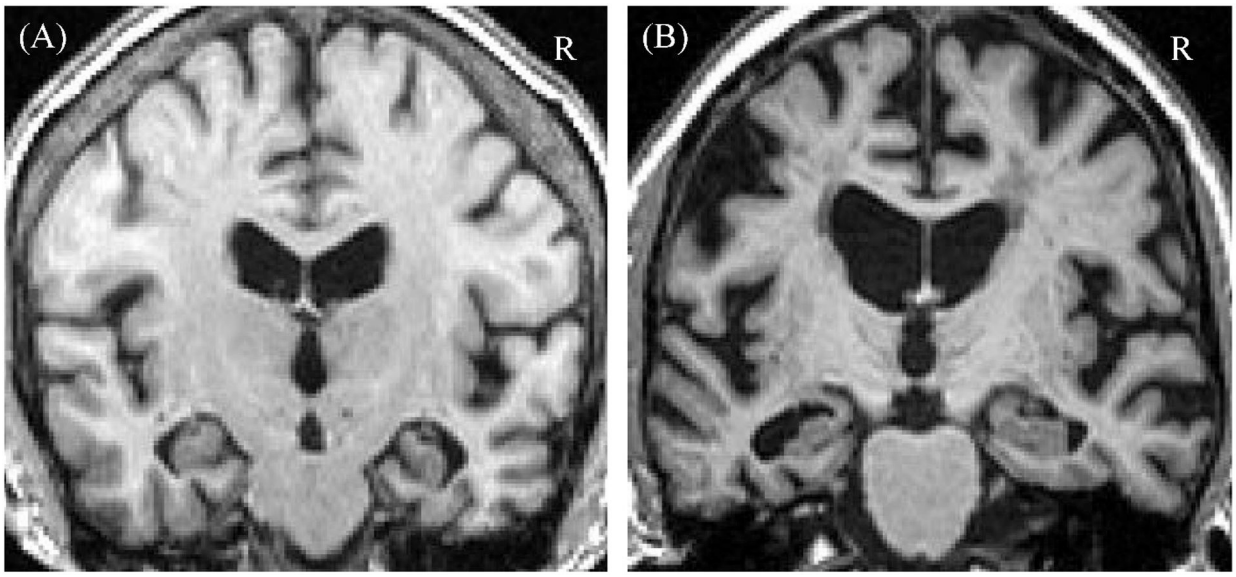


Figure 1. Example MRI Scans Showing Normal Aging and Cortical Atrophy

Structural T1-weighted MRI scan for a normal older adult control (A) and a patient with Alzheimer's disease (B) with significant atrophy are shown. Scans are examples taken from data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). MRI-magnetic resonance imaging; R = right

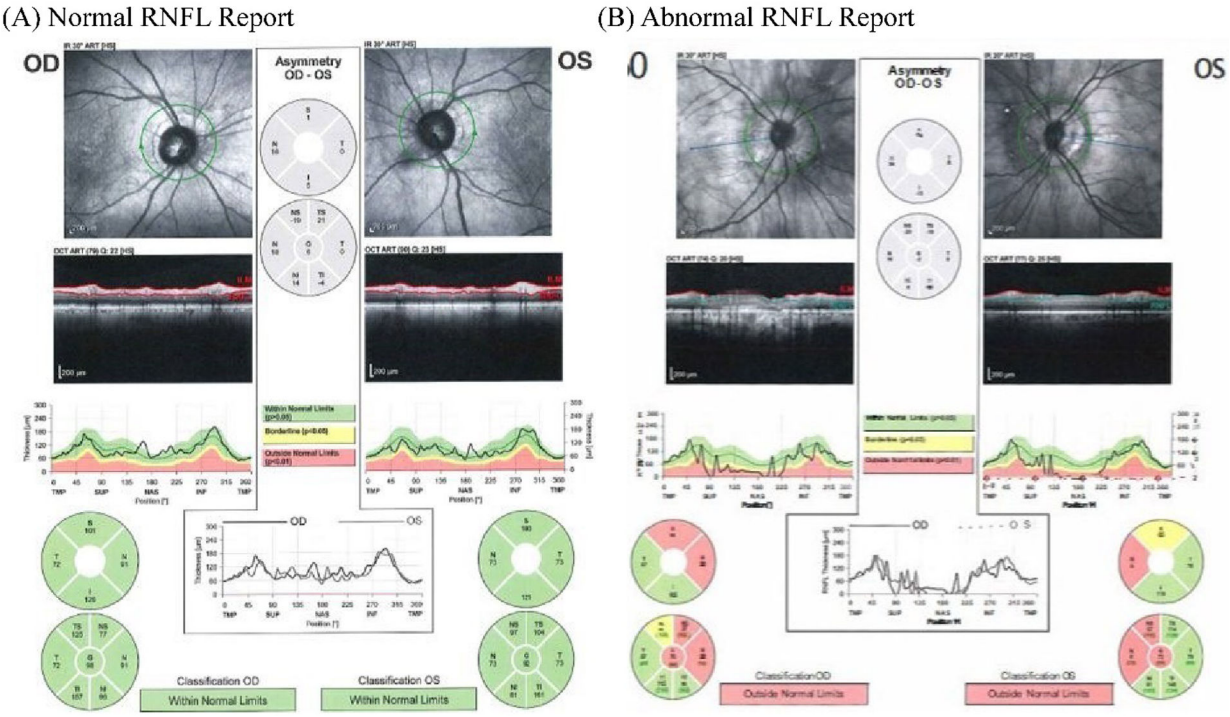
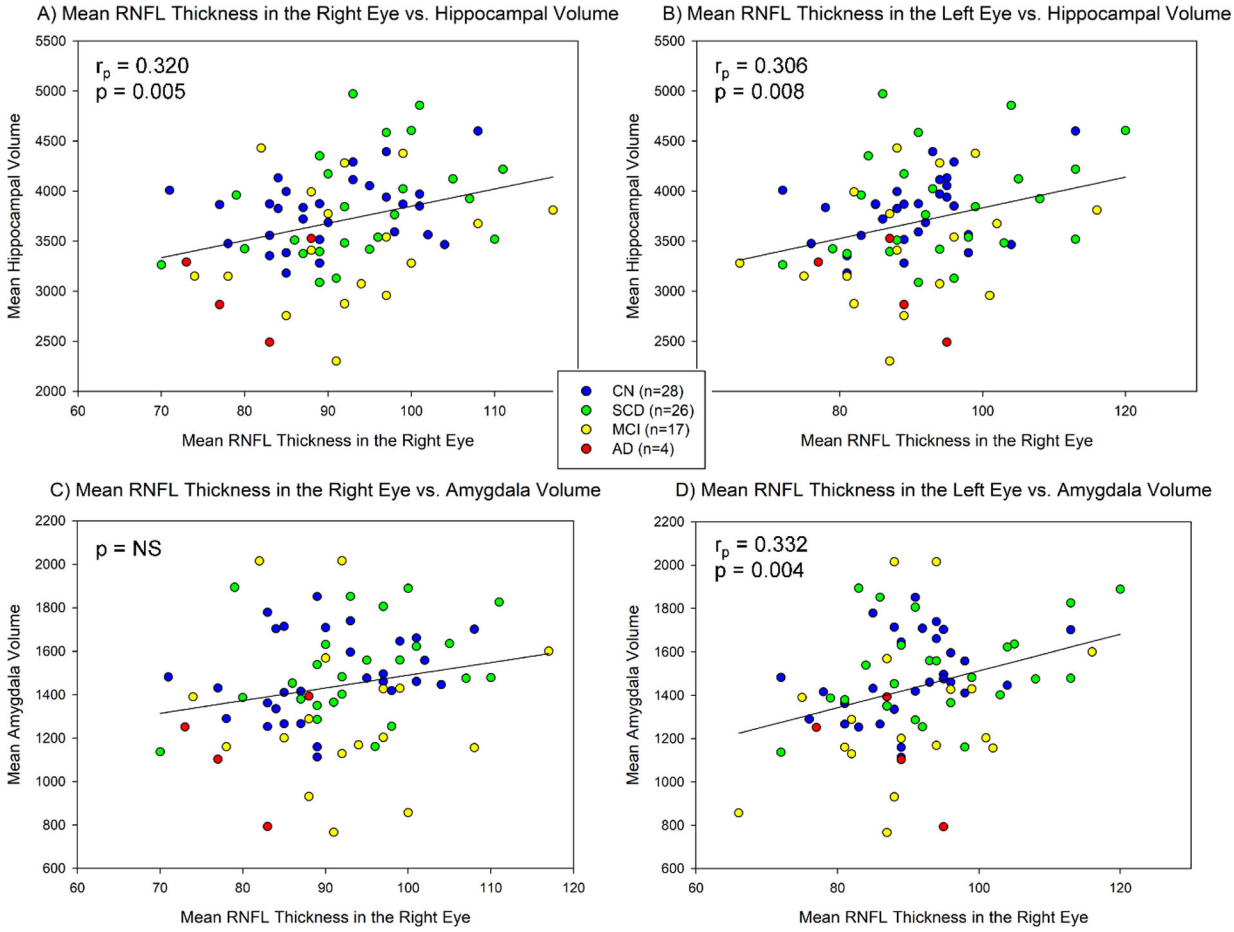


Figure 2. Example Optical Coherence Tomography of the RNFL

Example reports from OCT assessment of the RNFL are shown, including a normal evaluation (A) and an abnormal evaluation (B). OCT-Optical coherence tomography; RNFL-retinal nerve fiber layer



Figures 3. Association Between Mean RNFL Thickness and Hippocampal and Amygdalar Atrophy in the Full Sample

Significant associations between mean RNFL thickness in the right (A) and left (B) eyes and bilateral mean hippocampal volume are observed ($p<0.05$ corrected). In addition, a significant association between bilateral mean amygdalar volume and mean RNFL thickness in the left eye (D), but not the right eye (C), was also observed ($p<0.05$ corrected). The analysis includes the full sample (n=75, 28 CN, 26 SCD, 17 MCI, 4 AD). AD – Alzheimer's disease; CN – cognitively normal older adult; MCI – mild cognitive impairment (MCI); NS – not significant; RNFL = retinal nerve fiber layer; SCD = subjective cognitive decline

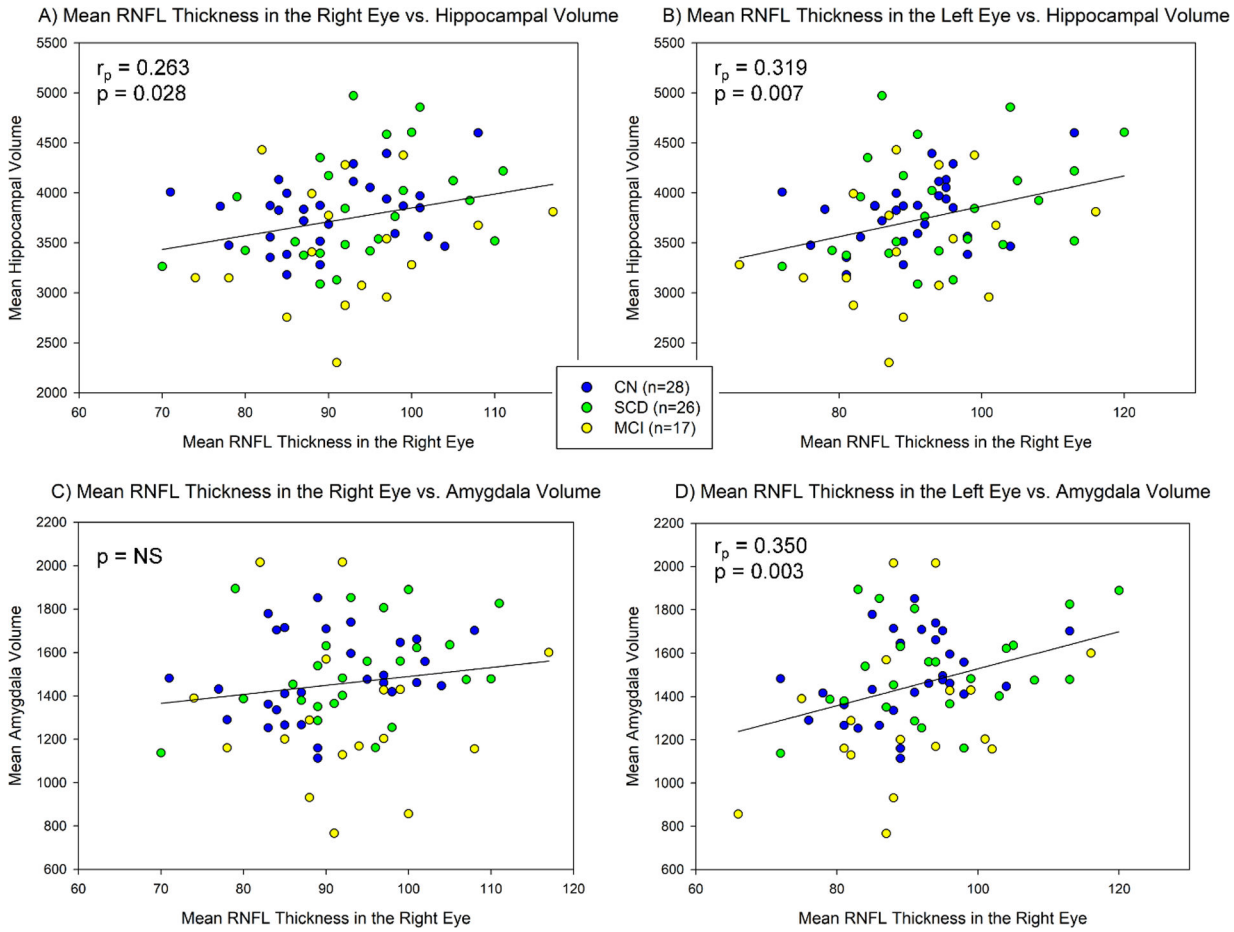


Figure 4. Association Between Mean RNFL Thickness and Hippocampal and Amygdalar Atrophy in the Non-Alzheimer's Disease Subsample

In the subsample, significant associations between mean RNFL thickness in the right (A) and left (B) eyes and bilateral mean hippocampal volume are observed ($p<0.05$ corrected). A significant association was also observed between bilateral mean amygdalar volume and mean RNFL thickness in the left eye (D), but not the right eye (C; $p<0.05$ corrected). The analysis excludes the 4 AD patients, including only participants at-risk or prodromal stages (n=71, 28 CN, 26 SCD, 17 MCI). AD – Alzheimer's disease; CN – cognitively normal older adult; MCI – mild cognitive impairment (MCI); NS – not significant; RNFL = retinal nerve fiber layer; SCD = subjective cognitive decline

Table 1.

Demographic and Clinical Data (Mean (Standard Deviation))

	CN (N=28)	SCD (N=26)	MCI (N=17)	AD (N=4)	p-value
Age (years)	70.5 (5.8)	71.0 (5.6)	73.8 (7.5)	68.6 (12.0)	0.331
Sex (M, F) *	6, 22	11, 15	10, 7	3, 1	**<0.001**
Ethnicity/Race * (% Non-Hispanic White)	82%	75%	94%	75%	0.701
IOP-RE (mmHg)	14.5 (2.5)	16.3 (3.2)	16.2 (2.8)	16.8 (5.1)	0.377
IOP-LE (mmHg)	14.5 (2.3)	16.1 (3.3)	16.6 (2.6)	16.5 (5.0)	0.089
APOE Genotype *,1 (% ε4 positive)	46.4%	48.0%	56.3%	75.0%	0.173
Rey AVLT Immediate	47.0 (7.5)	44.0 (8.2)	32.5 (8.1)	24.5 (4.9)	**<0.001**
Rey AVLT Delayed	9.9 (2.7)	9.3 (3.2)	3.9 (3.5)	0.0 (0.0)	**<0.001**
MoCA Total Score	26.4 (2.1)	25.4 (3.8)	20.6 (4.0)	15.5 (7.0)	**<0.001**
CDR-Sum of Boxes	0.04 (0.1)	0.2 (0.4)	1.1 (1.2)	3.5 (1.4)	**<0.001**
Self: CCI Total	25.7 (5.6)	41.7 (11.8)	54.9 (17.2)	58.3 (11.5)	**<0.001**
Informant: CCI Total	26.3 (9.7)	28.4 (8.3)	53.9 (17.9)	76.8 (15.6)	**<0.001**

* P-values result from a Pearson Chi-Square test (the rest are analyses of covariance (ANCOVAs))

1 APOE genotyping missing for 1

CN: cognitively normal; SCD: subjective cognitive decline; MCI: mild cognitive impairment; AD: Alzheimer's disease; IOP- Intraocular pressure; in mm of Hg; RE-Right eye; LE- Left eye; Rey AVLT- Rey Auditory Verbal Learning test; MoCA: Montreal Cognitive Assessment, CDR: Clinical Dementia Rating Test; CCI = 20-item Cognitive Change Index

Table 2.

Macular and Retinal Nerve Fiber Layer Thickness by Group (Mean (Standard Deviation))

	CN (N=28)	SCD (N=26)	MCI (N=17)	AD (N=4)	p-value
RE: Macula	271.6 (21.9)	282.3 (21.5)	278.9 (15.0)	285.5 (35.5)	0.294
LE: Macula	288.0 (10.9)	281.2 (10.7)	288.6 (13.4)	296.8 (55.6)	0.936
RE: Temporal RNFL Thickness	70.5 (11.0)	68.3 (14.7)	74.4 (16.1)	73.5 (15.9)	0.554
RE: Nasal RNFL Thickness	65.6 (14.5)	72.7 (16.4)	67.9 (14.5)	60.3 (13.3)	0.256
RE: Inferior RNFL Thickness	107.8 (16.8)	110.0 (17.8)	109.1 (16.7)	91.0 (11.0)	0.226
RE: Superior RNFL Thickness	114.1 (26.3)	120.7 (20.4)	118.6 (15.7)	97.0 (8.6)	0.204
RE: Mean RNFL Thickness	90.4 (8.9)	93.0 (9.6)	92.5 (10.4)	80.3 (6.6)	0.089
LE: Temporal RNFL Thickness	68.9 (12.0)	66.8 (13.0)	63.8 (11.8)	76.8 (22.1)	0.288
LE: Nasal RNFL Thickness	62.4 (13.9)	72.9 (21.5)	70.9 (11.9)	60.5 (3.8)	0.085
LE: Inferior RNFL Thickness	109.8 (13.8)	114.4 (18.0)	103.7 (18.3)	103.8 (15.3)	0.191
LE: Superior RNFL Thickness	121.4 (16.8)	126.4 (18.0)	120.7 (18.6)	107.0 (8.7)	0.202
LE: Mean RNFL Thickness	90.3 (8.5)	95.1 (12.2)	89.8 (11.5)	87.0 (7.4)	0.220

Values for both macular and RNFL thickness are measured in μm.

CN: cognitively normal; SCD: subjective cognitive decline; MCI: mild cognitive impairment; AD: Alzheimer's disease; RE-Right eye; LE- Left eye; RNFL: Retinal Nerve Fiber Layer.

Table 3.

Association of RNFL Thickness and Brain Volumes

		RNFL Thickness Measures									
		RE Avg	**RE Temp**	**RE Inf**	**RE Nasal**	**RE Sup**	**LE Avg**	**LE Temp**	**LE Inf**	**LE Nasal**	**LE Sup**
Brain Volume Measures	Global Vol	0.235 (0.046)	ns	ns	0.276 (0.018)	ns	0.244 (0.037)	ns	0.231 (0.049)	ns	ns
	Temporal lobe Vol	0.242 (0.039)	ns	ns	0.230 (0.050)	ns	0.290 (0.013)	ns	0.270 (0.021)	ns	0.241 (0.040)
	LTL Vol	0.249 (0.034)	ns	ns	0.244 (0.038)	ns	0.298 (0.011)	ns	0.281 (0.016)	ns	0.253 (0.031)
	MTL Vol	ns	ns	ns	ns	ns	0.231 (0.049)	ns	ns	ns	ns
	Hippocampal Vol	**0.320** (**0.005**)	ns	0.280 (0.016)	ns	ns	**0.306** (**0.008**)	ns	0.279 (0.016)	ns	ns
	Amygdala Vol	ns	ns	ns	ns	ns	**0.332** (**0.004**)	ns	0.296 (0.010)	ns	0.282 (0.015)
	Cingulate Vol	0.244 (0.037)	ns	ns	ns	ns	ns	ns	0.299 (0.010)	ns	ns
	Occipital lobe Vol	0.264 (0.024)	ns	ns	0.279 (0.017)	ns	ns	ns	ns	ns	ns
	Frontal lobe Vol	ns	ns	ns	0.242 (0.039)	ns	ns	ns	ns	ns	ns
	Parietal Vol	ns	ns	ns	0.300 (0.010)	ns	ns	ns	ns	0.236 (0.044)	ns

Values represent r (p) values; Multiple comparison corrected p-value = 0.008 in bold.

Avg-Average; Inf-Inferior; LE- Left eye; LTL- Lateral temporal lobe; MTL- Medial temporal lobe; ns = not significant at uncorrected p<0.05; RE-Right eye; RNFL- Retinal nerve fiber layer; Sup-superior; Temp-Temporal; Vol-Volume