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RESEARCH ARTICLE

Optical Coherence Tomography in Alzheimer's Disease: A Meta-Analysis

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Abstract

Background

Alzheimer's disease (AD) is a neurodegenerative disorder, which is likely to start as mild cognitive impairment (MCI) several years before the its full-blown clinical manifestation. Optical coherence tomography (OCT) has been used to detect a loss in peripapillary retina nerve fiber layer (RNFL) and a reduction in macular thickness and volume of people affected by MCI or AD. Here, we performed an aggregate meta-analysis combining results from different studies.

Methods and Findings

Data sources were case-control studies published between January 2001 and August 2014 (identified through PubMed and Google Scholar databases) that examined the RNFL thickness by means of OCT in AD and MCI patients compared with cognitively healthy controls.

Results

11 studies were identified, including 380 patients with AD, 68 with MCI and 293 healthy controls (HC). The studies suggest that the mean RNFL thickness is reduced in MCI (weighted mean differences in μ m, WMD = -13.39, 95% CI: -17.34 to -9.45, p = 0.031) and, even more so, in AD (WMD = -15.95, 95% CI: -21.65 to -10.21, p<0.0001) patients compared to HC. RNFL in the 4 quadrants were all significantly thinner in AD superior (superior WMD = -24.0, 95% CI: -34.9 to -13.1, p<0.0001; inferior WMD = -20.8, 95% CI: -32.0 to -9.7, p<0.0001; nasal WMD = -14.7, 95% CI: -23.9 to -5.5, p<0.0001; and temporal WMD = -10.7, 95% CI: -19.9 to -1.4, p<0.0001); the same significant reduction in quadrant RNFL was observed in MCI patients compared with HC (Inferior WMD = -20.22, 95% CI: -30.41 to -10.03, p = 0.0001; nasal WMD = -7.4, 95% CI: -10.08 to -4.7, p = 0.0000; and temporal WMD = -6.88,



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Data Availability Statement: This is a meta-analysis of previously published data. All the collected information are in the <u>Table 1</u> of the present meta-analysis.

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95% CI: -12.62 to -1.13, p = 0.01), with the exception of superior quadrant (WMD = -19.45, 95% CI: -40.23 to 1.32, p = 0.06).

Conclusion

Results from the meta-analysis support the important role of OCT for RNFL analysis in monitoring the progression of AD and in assessing the effectiveness of purported AD treatments.

Introduction

Amongst the various possible causes of dementia, Alzheimer's disease (AD) is the most common with an incidence that exponentially increases with age. AD is a brain degenerative disorder, where complex relationships between inherited susceptibility and environmental factors may play roles [1,2]. Because of the slowness of the disease's progression, the neurodegenerative processes are likely to start many years before the full-blown clinical manifestation of AD. This variable transitional phase is clinically recognized as a separate entity, mild cognitive impairment (MCI) [3]. Cognitive and functional severity within the MCI definition varies over a wide range, so that the syndrome of MCI is not clinically homogeneous [4]. Although subjects with MCI have an increased risk of progressing to dementia, most remain stable or return to normality [5].

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

Various visual disturbances may affect AD patients [6-13], which have been historically attributed to damage and/or degenerative processes in primary and associative visual cortical areas [14-18]. However, during the last few decades, some authors realized that cortical dysfunctions alone cannot explain entirely the pattern of observed defects [19]. Specifically, multiple forms of evidence points toward the involvement of retinal ganglion cells and their axons in the optic nerve as a basis of the visual dysfunction in AD [20,21]. In fact, histopathological lesions associated with AD—neuronal loss, beta-amyloid plaques, neurofibrillary tangles, and granulovacuolar degeneration—have been seen not only in brain structures historically thought to be involved in AD [15,16], but also within the neuroretina [20,22].

In the last two decades, several studies have searched for in vivo evidence of the retinal involvement in AD pathophysiology. Sophisticated imaging techniques have been used, including Optical Coherence Tomography (OCT) which has been extensively used to assess the morphological changes of the retina in AD and other dementing disorders. OCT permits the objective quantification in vivo of the retinal nerve fiber layer (RNFL) that consists of axons that form the optic nerve axons and contributes partially to the retinal thickness. This method consists of a non-invasive technology that allows for imaging of the eye [23,24]. Taking in mind that the human eye is an embryological protrusion of the brain, and the nerves and axons of the RNFL is a tract of the brain, it is not surprising that OCT has been widely employed in assessing RNFL thickness in several neurological disorders [25-30]. The OCT technique for the measurement of the peripapillary RNFL, the macular thickness and volume, has been proven useful for the detection of significant reduced retinal thickness in patients with AD [31-36] and in those affected with MCI [37]. Because early diagnosis of AD remains a big challenge, since up to now can be definitively confirmed only with post mortem histopathology, the discovery of new non-invasive in vivo biological markers is a major aim in current research on AD [38]. In this context, reduced retinal thickness measured with OCT may be a

promising biomarker for monitoring progression from normal and abnormal age-related processes, such as for instance supranuclear cataract and opacities of ocular lens, to the pathological neural degeneration undoubtedly associated with MCI and AD [39]. However, an aggregate analysis combining results from different studies is lacking. It is thus of particular interest to assess whether the retinal morphological changes may be related to cognitive impairment. Only a few published works have attempted correlations between the loss in RNFL and the neuropsychological indexes of cognitive impairment reported so the results are inconclusive [40-44].

The intent of this study is to provide a comprehensive meta-analysis overview of the available results provided by the OCT technique as used to understand morphological retinal changes that occur due to the degenerative processes associated with AD and MCI.

Materials and Methods

We followed methodology already published elsewhere [45]. In performing this meta-analysis we followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (S1 Fig) [46]. We initially searched the PubMed database to identify articles published up to August 2014. The search terms used were "Alzheimer's disease", "Dementia", "Optical coherence tomography", and "retinal nerve fiber layer", alone and in combination. The literature search was updated using the additional keywords "Alzheimer's disease", "electroretinogram" and "visual evoked potentials" to identify full-text papers written in English and published in peer-reviewed journals up to August 2014, using the PubMed and Google Scholar databases. In addition, we manually searched the reference lists of all primary articles and review articles. The initial search identified 14 articles (S1 Fig).

Inclusion and exclusion criteria

For inclusion in the meta-analysis a study had to meet the following criteria: (1) case-control or cross-sectional design; (2) OCT data were reported as mean or standard deviation; (3) AD and MCI patients were diagnosed according to established diagnostic systems (DSM-III, DSM-IV, ICD 9, ICD 10); (4) studies should provide the data of peripapillary and/or macular RNFL thickness; and (5) sample size \geq 9 in each group. (5) Only published studies were included, abstracts were ignored.

We used a two-step selection processes to identify eligible studies. In the first step, two investigators (GC, VP) screened the title and abstracts and by consensus identified all studies that did not meet any of the prespecified criteria. We excluded these studies. In the second step, the same investigators evaluated the full text versions of the remaining studies. Studies were excluded if they did not meet all criteria.

Data extraction

Two investigators (GC, LZ) independently extracted data and entered them in a customised database. Disagreements were resolved by consensus. The extracted data included authors and title of study, year of publication, study design, study size, study participants (AD, MCI, controls), mean age of the participants, severity of the disease (as assessed by MMSE or as classified in mild, moderate or severe AD), and OCT apparatus type. The parapapillary RNFL thickness parameters evaluated in these studies were average thickness (360° measurement), temporal quadrant thickness (316–45°), superior quadrant thickness (46–135°), nasal quadrant thickness (136–225°) and inferior quadrant thickness (226–315°). All data were extracted from the published studies and we did not contact the authors for further information.

Statistical analysis

Original data were obtained from the articles as much as possible. Data that could not be obtained were calculated when necessary. When standard deviation (SD) was not available, it was calculated using the sample sizes, standard error or, if not available, by extrapolating data from the bar chart. Statistical analysis was performed using custom written software in Mat-Lab environment (www.mathwork.com) and R statistical software (The R Foundation for statistical Computing v3.1.2). Summary estimates, including 95% confidence intervals (CIs), were calculated. For continuous outcome, means and standard deviations were used to calculate the weighted mean difference using a random-effects model (WMD). The chi-square test, tau² and the Higgins I^2 test were used to assess heterogeneity [47]. The I^2 test is a method for quantifying inconsistency across studies and describes the percentage of variability in effect estimates that is due to heterogeneity. A value greater than 50% was considered as substantial heterogeneity. If there was no heterogeneity across studies (P>0.1, I^2 ,50%), we adopt fixed-effects model for analysis. Otherwise, random-effects model was used. Potential publication bias was examined using a funnel plot [48]. A P value less than 0.05 was considered statistically significant. A strong correlation between sample size and summary estimates suggests publication bias.

Results

A total of 14 articles were initially identified; 2 articles were excluded due to duplications, and 1 article due to lack of data. We identified 11 articles on OCT in AD, of which 3 also contained data inMCI, that were suitable for analysis (see <u>Table 1</u>). However, 2 out of 11 articles were considered twice [36],[49] in the analysis due to the fact that the participants were scanned twice, with different OCT apparatus type. Overall, from the 11 studies we included a total of 380 patients with AD, 68 with MCI and 293 healthy controls. For the mean RNFL we identified 10 studies suitable for analysis, which included 349 AD patients, 68 MCI patients, and 263 healthy volunteers. For the quadrant RNFL we identified 8 studies suitable for analysis, which included 301 AD patients, 45 MCI patients, and 225 healthy controls. The articles included are described in <u>Table 1</u> and the main results of the meta-analysis are summarised in Figs <u>1</u> and <u>2</u>.

Meta-analysis of OCT data in AD patients

Analysis of mean RNFL thickness in 11 studies between AD patients and healthy controls found significant heterogeneity ($I^2 = 95.65\%$) across the studies, so the data were pooled through the random effects model. The meta-analysis of these data showed that the mean RNFL thickness in AD was reduced significantly compared with healthy controls (WMD = -15.95, 95% CI: -21.65 to -10.21, p<0.0001, Fig 1). Moreover meta-analysis of each quadrant data showed that there was overall good heterogeneity across studies and a significant difference of RNFL thickness between the two groups in the all 4 quadrants: superior ($I^2 = 92.80\%$, WMD = -24.0, 95% CI: -34.9 to -13.1, p<0.0001), inferior ($I^2 = 90.62\%$, WMD = -20.8, 95% CI: -32.0 to -9.7, p<0.0001), nasal ($I^2 = 91.89\%$, WMD = -14.7, 95% CI: -23.9 to -5.5, p<0.0001), and temporal ($I^2 = 91.26\%$, WMD = -10.7, 95% CI: -19.9 to -1.4, p<0.0001) quadrants. In summary, the results of meta-analysis showed that there was a significant RNFL thickness reduction in all quadrants in AD patients compared with the control group.

Meta-analysis of OCT data in MCI patients

Analysis of mean RNFL thickness in 3 studies between MCI patients and healthy controls found less, but still significant, heterogeneity ($I^2 = 70.99\%$) across the studies, so the data were

Table 1. Den	nographic dat	ta and retinal	Table 1. Demographic data and retinal NFL thicknes	ss measuremen	ts in patients an	is measurements in patients and controls as determined by OCT.	srmined by OCT.			
Reference	No. Of subjects and diagnosis	Mean MMSE/ AD stage	Mean age ± SD	OCT machine	Mean NFL (µm)	Superior quadrant (µm)	Inferior quadrant (µm)	Nasal quadrant (µm)	Temporal quadrant (µm)	Note
Parisi et al.	17 AD	/mild	70.37 ± 6.1	Humphrey	59.5±16.70*	72.1 ± 21.4*	77.9±26.4*	50.4±23.2*	37.9±17.60*	NFL overall values
31,32	14 controls				99.9 ± 8.95	104.6 ± 12.1	116.2±9.87	93.4±13.7	85.6±8.21	correlated with PERG
lseri et al. [60]	14 AD	18.5/mild to moderate	70.1 ± 9.7	Carl Zeiss Meditec, Model 3000	87.4 ± 23.7*	112.6 ± 35.3*	103.1 ± 33.6*	63.5 ± 19.1*	64.9 ± 17.7	Decline in both peripapillary and macular thickness
	15 controls	29.4	65.1 ± 9.8		113.1 ± 6.7	137.1 ± 16.4	141.5 ± 19.1	96.0 ± 34.4	72.3 ± 16.4	and volume in AD eyes
Berisha et al. [64]	9 AD	23.8/mild to moderate	74.3 ± 3.3	Carl Zeiss Meditec, Model 3000		92.2 ± 21.6*	117.0 ± 15.3	67.0 ± 15.0	65.7 ± 15.1	Narrowing of the retinal microvasculature
	8 HV	29.5	74.3 ± 5.8			113.6±10.8	128.1 ± 11.4	69.5 ± 11.1	64.1 ± 7.3	
Paquet	23 MCI	28.8	78.7 ± 6.2	Carl Zeiss	89.3±2.7*					The involvement of
et al. 33	14 AD 12 AD	22.6/mild 16.6/ severe	78.3 ± 5.1 78.8 ± 4.9	Stratus OCI 3	89.2 ± 2.9* 76.6 ± 3.8*					retina is an early event in the course of this disorder
	15 controls	28.9	75.5 ± 5.1		102.2 ± 1.8					
Lu et al.	22 AD		73 ± 8	Carl Zeiss	90 ± 18*(§)	107 ± 30*(§)	116 ± 35*(§)	66 ± 26	70 ± 20	Enlarged optic cup to
34	22 controls		68 ± 9	Meditec, Model 3000	98 ± 12	124 ± 16	128 ± 18	70 ± 17	71 ± 13	disc ratio in AD
Kesler	24 MCI	28.1	71.0 ± 10.0	Carl Zeiss	85.8±10.0*	101.3 ± 15.2	111.9 ± 16.1*	65.9 ± 15.1	64.2 ± 13.9	RNFL thickness not
et al. [<u>37</u>]	30 AD	23.6	73.7 ± 9.9	Stratus OCT	84.7 ± 10.6*	99.0 ± 18.0*	110.1 ± 19.1*	66.8 ± 14.5	61.7 ± 10.9	correlated with MMSE
	24 controls		70.9 ± 9.2	'n	94.3±11.3	110.0 ± 16.7	127.0 ± 15.5	76.4 ± 21.8	67.8 ± 15.1	
Moreno-	10 AD	16.4	73.0 ± 6.5	TOPCON 3D	$94.5 \pm 2.2^{*}$					Retinal involvement
Ramos et al. [61]	10 LB	14.9	74.2 ± 5.1	OCT-1000	93.3 ± 1.5*					measured by OCT mav also be present
	10 PD	16.4	74.3 ± 5.0		94.8±2.0*					in non-AD dementias
	10 controls	29.2	70.2±5.5		108.0 ± 2.2					
Marziani et al. [<u>36]</u>	21 AD	19.9/mild to moderate	79.3 ± 5.7	(1) Optovue RTVue-100	244.1 ± 17.9 ¹					Reduced RNFL in AD patients using 2 different OCT
					277.5 ± 21.7^2					instruments
	21 controls	27.9	77.0 ± 4.2	(2) Spectralis Heidelberg Engineering	252.3 ± 19.2¹ ç					
					283.8 ± 27.3² ç					
Kirbas	40 AD	21.5	69.3 ± 4.9	Spectral	65 ± 6.2*	76 ± 6.7*	106 ± 11.5	75 ± 2.8	74 ± 6.7	No correlation
et al. [<u>35</u>]	40 controls		68.9 ± 5.1	domain OCT	75 ± 3.8	105 ± 4.8	108 ± 8.7	76 ± 2.7	77 ± 7.3	between MMSE and OCT results

(Continued)

Reference	No. Of subjects and diagnosis	Mean MMSE/ AD stage	Mean age ± SD	OCT machine	Mean NFL (µm)	Superior quadrant (µm)	Inferior quadrant (µm)	Nasal quadrant (µm)	Temporal quadrant (µm)	Note
Larrosa et al. [49]	151 AD	18.31	75.29	(1) Carl Zeiss Meditec Cirrus	97.5 ± 14.1 ¹	113.2 ± 18.7 ¹ *	120.4 ± 20.1 ¹ *	72.7 ± 17.3 ¹	64.5 ± 21.7 ¹ *	RNFL measurements were a very useful and precise tool for
					98.2 ± 17.1 ² *					AD diagnosis.
	61 controls		74.87	(2) Spectralis Heidelberg Engineering	100.5 ± 13.0 ¹	117.8 ± 19.0 ¹ *	127.4 ± 21.0 ¹	74.5 ± 17.2 ¹	67.8 ± 20.0 ¹	
					102.7 ± 6.7^2					
Ascaso et al. [44]	21 aMCI	19.3	72.1 (AD +aMCI)	Stratus OCT 3	86.0±7.2*#	96.7 ± 14.6*	110.1 ± 17.7*	71.0 ± 16.7 ∗	66.3 ± 12.1 *	A significant association between
	18 AD				64.7 ± 15.2* ** #	73.2 ± 22.0* **	86.2 ± 25.7* **	43.3 ± 20.4 * **	56.7 ± 14.9 * **	RNFL thickness in superior and nasal
	41 controls	28.8	72.9		103.6 ± 8.9 #	126.6 ± 13.8	135.6 ± 17.6	77.8 ± 16.7	75.8 ± 16.6	quadrants, and MMSE score
AD, Alzheim	ier's disease; al	MCI, amnesti	AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; LB, de	/e impairment; LE	3, dementia with	Lewy bodies; MCI,	, mild cognitive imp	pairment; MMSF	E, mini mental st	AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; LB, dementia with Lewy bodies; MCI, mild cognitive impairment; MMSE, mini mental state examination; RNFL,

۲FL, retinal nerve fiber layer; PD, dementia associated with Parkinson's disease;

*, significantly different from controls;

**, significantly different from MCI;

[§] data extrapolated from the bar chart;

 $^{\rm 1}$ or 2 refer to the corresponding OCT machine;

ç Central sector;

* data showed from the right eye only.

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Table 1. (Continued)



AD patients

Healthy controls

Mean RNFL

Parisi et al., 2001	mean											
arisi et al., 2001	mean	SD	N	mean	SD	N	Mean Difference	CI 95	%	Weight %		
	59.5	16.7	17	99.9	9.0	14	-40.4	-49.62	-31.18	7.79	→	
eri et al., 2006	87.4	23.7	14	113.1	6.7	15	-25.7	-38.57	-12.83	6.54		
aquet et al., 2007 u et al., 2010	76.6 90.0	3.8 18.0	12 22	102.2 98.0	1.8 12.0	15 22	-25.6 -8.0	-27.94 -17.04	-23.26 1.04	9.61 7.85		
u et al., 2010 esler et al., 2011	90.0	10.6	30	98.0	11.3	22	-8.0	-17.04	-3.70	8.84		
Aoreno-Ramos et al., 2013	94.5	2.2	10	108.0	2.2	10	-13.5	-15.43	-11.57	9.65	-	
vlarziani et al., 2013(a)	244.1	17.9	21	252.3	19.2	21	-8.2	-19.43	3.03	7.10		4
Marziani et al., 2013(b)	277.5	21.7	21	283.8	27.3	21	-6.3	-21.22	8.62	5.87	·	
(irbas et al., 2013	65.0	6.2	40	75.0	3.8	40	-10.0	-12.25	-7.75	9.62	-	
arrosa et al., 2014(a)	97.5	14.1	151	100.5	13.0	61	-3.0	-6.96	0.96	9.33	H B -1	
arrosa et al., 2014(b)	98.2	17.1	151	102.7	6.8	61	-4.5	-7.72	-1.28	9.47		
Ascaso et al., 2014	64.7	15.2	18	103.6	8.9	41	-38.9	-46.43	-31.37	8.35		
Total			507			345	-15.93	-21.65	-10.21		+	
Overall effect	Z -5.46	P 0.0000		Heterogen	eity: Tau²a	: 87 32- Chi2=2	52.73, df= 11 (p<0.00001);	P= 95 65%		-60.00	-40.00 -20.00 0.0	0 20.00
					,.						Favours AD	Favours
Superior quadrant	AD patie			Healthy co								
	mean	SD	N	mean	SD	N	Mean Difference		95 %	Weight		
arisi et al., 2001	72.1	21.4	17	104.6	12.1	14	-32.5	-44.49	-20.51	12.49		
seri et al., 2006	112.6	35.3	14	137.1	16.4	15	-24.5	-44.77	-4.23	9.75		
lerisha et al., 2007 u et al., 2010	92.2 107.0	21.6 30.0	9 22	113.6 124.0	10.8 16.0	8 22	-21.4 -17.0	-37.37 -31.21	-5.43 -2.79	11.17		
u et al., 2010 esler et al., 2011	107.0	30.0 18.0	22 30	124.0	16.0 16.7	22	-17.0	-31.21	-2.79 -1.72	11.77 13.29		
irbas et al., 2013	76.0	6.7	40	105.0	4.8	24 40	-11.0	-20.28	-1.72	14.59		
arrosa et al., 2013	113.2	18.7	151	117.8	19.0	61	-4.6	-10.22	1.02	14.16		
scaso et al., 2014	73.2	22.0	18	126.6	13.8	41	-53.4	-64.41	-42.39	12.79		
otal			301			225	-24.0	-34.9	-13.1		-	
	z	Р								,		20.00
Overall effect	-4.32	0.0000		Heteroge	eneity: Tau	²= 209.84; Chi ²	=97.18, df= 7 (p<0.00001);	P= 92.80%		-00.	Favours AD	Favours
Inferior quadrant	AD patie	nts		Healthy c	ontrols							
	mean	SD	N	mean	SD	N	Mean Difference	C 1	95 %	Weight		
arisi et al., 2001	77.9	26.4	17	116.2	9.9	14	-38.3	-51.87	-24.73	12.13	→ →	
seri et al., 2006	103.1	33.6	14	141.5	19.1	15	-38.4	-58.48	-18.32	9.99	·	
erisha et al., 2007	117.0	15.3	9	128.1	11.4	8	-11.1	-23.84	1.64	12.39		
u et al., 2010	116.0	35.0	22	128.0	18.0	22	-12.0	-28.45	4.45	11.18		•
esler et al., 2011	110.1	19.1	30	127.0	15.5	24	-16.9	-26.13	-7.67	13.43		
irbas et al., 2013	106.0	11.5	40	108.0	8.7	40	-20.0	-6.47	2.47	14.45	-	
	120.4		151	127.4	21.0	61	-7.0	-13.17	-0.83	14.15		
		20.1										
	86.2	25.7	18	135.6	17.6	41	-49.4	-62.44	-36.36	12.30		
Ascaso et al., 2014	86.2	25.7			17.6	41 225			-36.36	12.30	•••• ••	
Larrosa et al., 2014(a) Ascaso et al., 2014 Fotal Overall effect			18	135.6		225	-49.4	-62.44 -32.0		12.30 	Pavours AD	Pavours
Ascaso et al., 2014 Fotal Dverall effect	86.2 Z -3.66	25.7 P 0.0002	18	135.6 Heteroge	eneity: Tau	225	-49.4 -20.8	-62.44 -32.0				avours
iscaso et al., 2014 otal Iverall effect	86.2 Z -3.66 AD patien	25.7 P 0.0002	18 301	135.6 Heteroge Healthy co	eneity: Tau ntrols	225 ²= 218.25; Chi²	-49.4 -20.8 =74.74, df= 7 (p<0.00001);	-62.44 -32.0 I ² = 90.63%	-9.7	-60.		Favours
iscaso et al., 2014 Total Overall effect Nasal Quadrant	Z -3.66 AD patien mean	25.7 P 0.0002 hts SD	18 301 N	135.6 Heteroge Healthy co mean	eneity: Tau ntrols SD	225 2= 218.25; Chi ² N	-49.4 -20.8 =74.74, df= 7 (p<0.00001); Mean Difference	-62.44 -32.0 I ² = 90.63%	-9.7 95 %	, Weight		Favours
sscaso et al., 2014 otal Viverall effect Nasal Quadrant arisi et al., 2001	2 -3.66 AD patien mean 50.4	25.7 P 0.0002 hts SD 23.2	18 301	135.6 Heteroge Healthy co mean 93.4	eneity: Tau ntrols SD 13.7	225 218.25; Chi ² <u>N</u> 14	-49,4 -20.8 =74.74, df= 7 (p<0.00001); Mean Difference -43.0	-62.44 -32.0 I ² = 90.63% <u>CI</u> -56.16	-9.7 95 % -29.84	 Weight 11.69	Favours AD	Favours
scaso et al., 2014 fotal Werall effect Nasal Quadrant arisi et al., 2001 Fert et al., 2006	2 -3.66 AD patien mean 50.4 63.5	25.7 P 0.0002 hts SD 23.2 19.1	18 301 N 17 14	Heteroge Healthy co mean 93.4 96	eneity: Tau ntrols SD	225 2 218.25; Chi ² N 14 15	-49.4 -20.8 =74.74, df= 7 (p<0.00001); Mean Difference -43.0 -32.5	-62.44 -32.0 I ² = 90.63% CI -56.16 -52.58	-9.7 95 % -29.84 -12.42	 Weight 11.69 8.87	Favours AD	Favours I
iscaso et al., 2014 iotal Werall effect Nasal Quadrant arisi et al., 2001 erisha et al., 2007	2 -3.66 AD patien mean 50.4 63.5 67	25.7 P 0.0002 hts SD 23.2 19.1 15	18 301 N 17 14 9	135.6 Heteroge Healthy co mean 93.4	eneity: Tau introls 5D 13.7 34.4 11.1	225 ² = 218.25; Chi ² N 14 15 8	-49,4 -20,8 =74,74, df= 7 (p<0.00001); Mean Difference -43,0 -32,5 -2,5	-62.44 -32.0 I ² = 90.63% CI -56.16 -52.58 -14.96	-9.7 95 % -29.84 -12.42 9.96	, Weight 11.69 8.87 11.99	Favours AD	Favours I
scaso et al., 2014 otal Verall effect Nasal Quadrant arisi et al., 2001 seri et al., 2006 erisha et al., 2007 ue tal., 2010	2 -3.66 AD patien mean 50.4 63.5	25.7 P 0.0002 hts SD 23.2 19.1	18 301 N 17 14	Heteroge Healthy co mean 93.4 96 69.5	eneity: Tau entrols SD 13.7 34.4	225 2 218.25; Chi ² N 14 15	-49.4 -20.8 =74.74, df= 7 (p<0.00001); Mean Difference -43.0 -32.5	-62.44 -32.0 I ² = 90.63% CI -56.16 -52.58	-9.7 95 % -29.84 -12.42	 Weight 11.69 8.87	Favours AD	Favours
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scaso et al., 2014 otal werall effect lasal Quadrant arisi et al., 2001 erisha et al., 2006 erisha et al., 2007 esier et al., 2007 esier et al., 2010 esier et al., 2013 arrosa et al., 2013	86.2 Z -3.66 AD patien mean 50.4 63.5 67 66 66.8 75 72.7	25.7 P 0.0002 tts 23.2 19.1 15 26 14.5 2.8 17.3	18 301 N 17 14 9 22 30 40 151	135.6 Heteroge Healthy co 93.4 96 69.5 70 76.4 76 74.5	ntrols 5D 13.7 34.4 11.1 21.8 2.7 17.2	225 22 218.25; Chi ² 24 22 24 40 61	-49.4 -20.8 =74.74, df= 7 (p<0.00001); -43.0 -43.0 -32.5 -2.5 -2.5 -4.0 -9.6 -1.0 -1.8	-62.44 -32.0 ≥ 90.63% (C) -56.16 -52.58 -14.96 -16.98 -19.75 -2.21 -6.92	-9.7 -29.84 -12.42 9.96 8.98 0.55 0.21 3.32	Weight 11.69 8.87 11.99 11.77 12.95 15.33 14.67	Favours AD	Favours I
scaso et al., 2014 otal verall effect lassal Quadrant arisi et al., 2001 seriet al., 2006 ierisha et al., 2007 ierisha et al., 2007 iesier et al., 2010 iesier et al., 2011 iribas et al., 2013 arrosa et al., 2013	86.2 Z -3.66 AD patien <u>mean</u> 50.4 63.5 67 66 66.8 75	25.7 P 0.0002 ats <u>SD</u> 23.2 19.1 15 26 14.5 2.8	18 301 N 17 14 9 22 30 40	135.6 Heteroge Healthy co 93.4 96 69.5 70 76.4 76	eneity: Tau entrols 5D 13.7 34.4 11.1 17 21.8 2.7	225 218.25; Chi ² N 14 15 8 22 24 40	-49.4 -20.8 =74.74, df= 7 (p<0.00001); Mean Difference -43.0 -32.5 -2.5 -4.0 -9.6 -1.0	-62.44 -32.0 I≥ 90.63% CI -56.16 -52.58 -14.96 -16.98 -19.75 -2.21	-9.7 -29.84 -12.42 9.96 8.98 0.55 0.21	weight 11.69 8.87 11.99 11.77 12.95 15.33	Favours AD	Favours I
Ascaso et al., 2014 Fotal	86.2 Z -3.66 AD patien 50.4 63.5 67 66 66 66.8 75 72.7 43.3	25.7 P 0.0002 tts 23.2 19.1 15 26 14.5 2.8 17.3 20.4	18 301 N 17 14 9 22 30 40 151	135.6 Heteroge Healthy co 93.4 96 69.5 70 76.4 76 74.5	ntrols 5D 13.7 34.4 11.1 21.8 2.7 17.2	225 22 218.25; Chi ² 24 22 24 40 61	-49.4 -20.8 =74.74, df= 7 (p<0.00001); -43.0 -43.0 -32.5 -2.5 -2.5 -4.0 -9.6 -1.0 -1.8	-62.44 -32.0 ≥ 90.63% (C) -56.16 -52.58 -14.96 -16.98 -19.75 -2.21 -6.92	-9.7 -29.84 -12.42 9.96 8.98 0.55 0.21 3.32	Weight 11.69 8.87 11.99 11.77 12.95 15.33 14.67	Favours AD	Favours
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kscaso et al., 2014 Total Dverall effect Varial effect Varial et al., 2001 seri et al., 2001 seri et al., 2005 bersha et al., 2007 u et al., 2010 (rester et al., 2010 (rester et al., 2013) arrosa et al., 2013 arrosa et al., 2014 (rotal	86.2 Z -3.66 AD patien <u>mean</u> 50.4 63.5 67 66.8 75 72.7 43.3 Z	25.7 P 0.0002 ats 5D 23.2 19.1 15 26 14.5 2.8 17.3 20.4 P 0.0017	18 301 N 17 14 9 22 30 40 151 18	135.6 Heelthy co <u>mean</u> 93.4 96 69.5 70 76.4 76 74.5 77.8	ntrols 5D 13.7 34.4 11.1 17 21.8 2.7 17.2 16.7 meity: Tau	225 ≥= 218.25; ChiP 14 15 15 8 22 24 40 61 41 225	-49.4 -20.8 =74.74, df= 7 (p<0.00001); -43.0 -32.5 -2.5 -4.0 -9.6 -1.0 -1.8 -34.5 -14.7	-62.44 -32.0 I≥ 90.63% -56.16 -52.58 -14.96 -16.98 -19.75 -2.21 -6.92 -45.22 -45.22 -23.9	-9.7 -29.84 -12.42 9.96 8.98 0.55 0.21 3.32 -23.78	Weight 11.69 8.87 11.99 11.77 12.95 15.33 14.67 12.72	Favours AD	Favours
scaso et al., 2014 otal werall effect lasal Quadrant arisi et al., 2001 erisha et al., 2007 u et al., 2010 erisha et al., 2010 esiser et al., 2011 irbas et al., 2013 arrosa et al., 2014 otal tverall effect	86.2 Z -3.66 AD patien mean 50.4 63.5 67 66 65.8 75.7 72.7 43.3 Z -3.14 AD patie	25.7 P 0.0002 tts 23.2 19.1 15 26 14.5 2.8 17.3 20.4 P 0.0017 nts	18 301 17 14 9 22 30 0 151 18 301	Heteroge Healthy co mean 95 95 96 95 70 76.4 76.4 76.4 76.5 77.8 Heteroge	ntrols 5D 13.7 34.4 11.1 17 21.8 2.7 17.2 16.7 sneity: Tau ontrols	225 № 218.25; Chi ² 14 15 8 22 24 40 61 41 225 ≈ 143.22; Chi ²	-49.4 -20.8 =74.74, df= 7 (p=0.00001); Mean Difference -43.0 -32.5 -2.5 -4.0 -32.5 -1.0 -1.0 -1.8 -34.5 -14.7 =86.36, df= 7 (p=0.00001);	-62.44 -32.0 I≥ 90.63% I≥ 90.63% I≥ 90.63% -55.58 -14.96 16.98 -19.75 -2.21 -6.92 -45.22 -23.9 I≥ 91.89%	-9.7 -29.84 -29.84 -12.42 9.96 8.98 8.98 0.55 0.55 0.55 0.55 -5.5		Favours AD	Favours
scaso et al., 2014 iotal iotal Werall effect Masal Quadrant arisi et al., 2001 terisha et al., 2007 u et al., 2010 esfer et al., 2010 esfer et al., 2011 iribas et al., 2014 iribas et al., 2014 iverall effect Pemporal quadrant	86.2 Z -3.66 AD patien <u>mean</u> 50.4 63.5 67 66.8 66.8 66.8 72.7 72.7 43.3 Z -3.14 AD patie	25.7 P 0.0002 ats 23.2 15 26 14.5 2.8 17.3 20.4 P 0.0017 nts SD	18 301 17 14 9 22 20 40 151 18 301 301	Heteroge Healthy co mean 93.4 96 69.5 70. 76. 74.5 77.8 Heteroge Healthy co mean	eneity: Tau ontrols 5D 13.7 34.4 11.1 17 21.8 2.7 17.2 16.7 meity: Tau ontrols 5D	225 ≈ 218.25; ChP 14 15 8 22 24 40 61 41 225 ≈ 143.22; ChP N	-49.4 -20.8 =74.74, df= 7 (p<0.00001); -43.0 -32.5 -2.5 -4.0 -9.6 -1.0 -1.8 -34.5 -14.7 =86.36, df= 7 (p<0.00001); Mean Difference	-62.44 -32.0 -32.0 -56.16 -52.58 -14.96 -16.98 -14.96 -16.92 -22.21 -6.92 -23.9 -23.9 -23.9 -23.9	-9.7 -29.84 -29.84 -12.84 9.96 8.98 0.55 0.21 3.32 -23.78 -5.5		Favours AD	Favours
scaso et al., 2014 fotal Verall effect Vasal Quadrant arisi et al., 2001 seri et al., 2006 erisha et al., 2007 u et al., 2010 esfer et al., 2007 u et al., 2010 esfer et al., 2001 arisa et al., 2014 werall effect emporal quadrant arisi et al., 2001	86.2 Z -3.66 AD patien mean 63.5 67 66 66.8 75 72.7 43.3 Z -3.14 AD patien 75 72.7 43.3	25.7 P 0.0002 sts 23.2 19.1 15 26 14.5 2.8 17.3 20.4 P 0.0017 nts <u>SD</u> 17.6	18 301 N 17 14 9 22 30 40 40 151 18 301 8 301 17	135.6 Heteroge Healthy co <u>mean</u> 93.4 96 99.5 70 76.4 76.7 76.7 77.8 Heteroge Healthy co <u>mean</u> 85.6	ntrols <u>SD</u> 13.7 36.4 11.1 17 21.8 2.7 16.7 16.7 16.7 science of the second	225 ≈ 218.25; Chi ² 14 15 8 22 24 40 61 41 225 ≈ 143.22; Chi ² N 14	-49.4 -20.8 =74.74, df= 7 (p<0.00001); -43.0 -43.0 -32.5 -2.5 -2.5 -4.0 -9.6 -1.0 -1.0 -1.8 -34.5 -14.7 =86.36, df= 7 (p<0.00001); Mean Difference -47.70	-62.44 -32.0 ≥ 90.63% ≥ 90.63% -56.16 -52.58 -14.96 -16.98 -19.75 -2.21 -6.92 -45.22 -23.9 ≥ 91.89% ≥ 91.89% ≥ 91.89%	-9.7 -29.84 -12.42 9.96 8.98 0.55 0.21 3.32 -23.78 -5.5 -5.5 -5.5	Weight 11.69 8.87 11.99 11.77 12.95 15.33 14.67 12.72 Weight 12.72	Favours AD	Favours
scaso et al., 2014 iotal iotal Verall effect larisi et al., 2001 seriet et al., 2006 ierishe et al., 2007 uet al., 2010 iesier et al., 2010 isser et al., 2010 isser et al., 2014 iotal Dverall effect iemporal quadrant arisi et al., 2001 seriet et al., 2001 ieriet et al., 2001	86.2 Z -3.66 AD patien 50.4 63.5 67 66 66.8 72.7 43.3 Z -3.14 AD patien mean 37.9 64.9	25.7 P 0.0002 23.2 19.1 15 26 14.5 2.8 17.3 20.4 P 0.0017 nts SD 17.6 17.7	18 301 17 14 9 22 30 40 40 151 18 301 8 301 N 17 14	135.6 Heteroge Healthy co mean 93.4 95 69.5 70 76.4 76.5 77.3 Heteroge Heteroge Healthy co mean 85.6 85.2,3	ntrols 5D 34.4 11.1 17 2.7 16.7 teneity: Tau controls 5D 8.2 16.4	225 ≥ 218.25; Chi ² 14 15 8 22 24 40 61 41 225 ≥ 143.22; Chi ² N 14 15	-49.4 -20.8 =74.74, df= 7 (p=0.00001); Mean Difference -43.0 -32.5 -2.5 -4.0 -32.5 -3.6 -1.0 -1.0 -1.8 -34.5 -14.7 =86.36, df= 7 (p=0.00001); Mean Difference -47.70 -7.40	-62.44 -32.0 P≥ 90.63% -56.16 -52.58 -14.96 -16.98 -19.75 -2.21 -6.92 -45.22 -23.9 P≥ 91.89% C(-57.11 -19.84	-9.7 -29.84 -12.42 9.96 8.98 8.98 8.95 0.55 0.55 0.55 0.55 -5.5 -5.5 -5.5		Favours AD	Favours
scaso et al., 2014 otal verall effect Nasal Quadrant arisi et al., 2001 seri et al., 2001 erisha et al., 2007 ester et al., 2010 ester et al., 2010 ester et al., 2011 infase et al., 2013 arrosa et al., 2014 verall effect Temporal quadrant arisi et al., 2006 erisha et al., 2007	86.2 Z -3.66 AD patien 50.4 63.5 67 66 66.8 75 72.7 43.3 Z -3.14 AD patien 2 37.9 64.9 65.7	25.7 P 0.0002 tts SD 23.2 19.1 15 26 14.5 2.6 17.3 20.4 P 0.0017 nts SD 17.6 17.7 15.1	18 301 17 14 9 9 22 30 0 151 18 301 301 N 17 14 9	135.6 Heteroge 93.4 96 69.5 70 76.4 76 74.5 77.8 Heteroge Healthy co <u>mean</u> 85.6 72.3 64.1	ntrols 50 13.7 34.4 11.1 17.7 17.2 16.7 16.7 sources 50 8.2 16.4 7.3	225 ≥ 218.25; Chi ² 14 15 8 22 24 40 61 41 225 ≥ 143.22; Chi ² N 14 15 8	-49.4 -20.8 =74.74, df= 7 (p<0.00001); -43.0 -32.5 -2.5 -4.0 -9.6 -1.0 -1.8 -34.5 -14.7 =86.36, df= 7 (p<0.00001); Mean Difference -47.70 -7.40 -6.60	-62.44 -32.0 2= 90.63% -56.16 -52.58 -14.96 -16.98 -19.75 -2.21 -6.92 -45.22 -23.9 2= 91.89% [2= 91.89% [2= 91.89%]	-9.7 -9.84 -12.42 9.96 8.98 0.55 0.21 3.32 -23.38 -5.5 -5.5 -38.29 5.04 12.69	Weight 11.69 8.87 11.99 11.77 12.95 15.33 14.67 12.72 .co Weight 12 11.22 11.71	Favours AD	Favours
scaso et al., 2014 iotal iotal Verall effect lassal Quadrant arisi et al., 2001 erisha et al., 2006 erisha et al., 2007 estar, 2010 estar, 2010 estar, 2013 arcsa et al., 2014 iotal Verall effect emporal quadrant arisi et al., 2001 serisha et al., 2001 serisha et al., 2001 serisha et al., 2001 serisha et al., 2007 u et al., 2010	86.2 Z -3.66 AD patien 50.4 63.5 67 66 66.8 72.7 43.3 Z -3.14 AD patien mean 37.9 64.9	25.7 P 0.0002 23.2 19.1 15 26 14.5 2.8 17.3 20.4 P 0.0017 nts SD 17.6 17.7	18 301 17 14 9 22 30 40 40 151 18 301 8 301 N 17 14	135.6 Heteroge Healthy co mean 93.4 95 69.5 70 76.4 76.5 77.3 Heteroge Heteroge Healthy co mean 85.6 85.2,3	ntrols 5D 34.4 11.1 17 2.7 16.7 teneity: Tau controls 5D 8.2 16.4	225 ≥ 218.25; Chi ² 14 15 8 22 24 40 61 41 225 ≥ 143.22; Chi ² N 14 15	-49.4 -20.8 =74.74, df= 7 (p=0.00001); Mean Difference -43.0 -32.5 -2.5 -4.0 -32.5 -3.6 -1.0 -1.0 -1.8 -34.5 -14.7 =86.36, df= 7 (p=0.00001); Mean Difference -47.70 -7.40	-62.44 -32.0 P≥ 90.63% -56.16 -52.58 -14.96 -16.98 -19.75 -2.21 -6.92 -45.22 -23.9 P≥ 91.89% C(-57.11 -19.84	-9.7 -29.84 -12.42 9.96 8.98 8.98 8.95 0.55 0.55 0.55 0.55 -5.5 -5.5 -5.5	Weight 11.69 8.87 11.99 11.77 12.95 15.33 14.67 12.72 Weight 12 11.27 12.21 	Favours AD	Favours
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Fig 1. Forest plots of weighted mean difference (WMD) of AD patients for the mean and each single quadrant RNFL. Horizontal lines are 95% confidence intervals.

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MCI patie	nts		Healthy co	ntrols							
mean	SD	N	mean	SD	N	Mean Difference	CI 9	5 %	Weight		
89.3	2.7	23	102.2	1.8	15	-12.90	-14.33	-11.47	45.57	HEH	
85.8	10.0	24	94.3	11.3	24	-8.50	-14.54	-2.46	22.69		
86.0	7.2	21	103.6	8.9	41	-17.60	-21.71	-13.49	31.74 ⊢		
		68			80	-13.39	-17.34	-9.45			
Z -6.66	P 0.0000		Heterop	geneity: Ta	u²= 8.34; Chi²=6	.90, df= 2 (p=0.0318); I ² =	70.99%		-25.00	-15.00 -5.00 0.0 Favours MCI	0 Favour
MCI patie	nts		Healthy cor	ntrols							
mean	SD	N	mean	SD	N	Mean Difference	CI 9	5%	Weight		<u> </u>
101.3	15.2	24	110	16.7	24	-8.70	-17.73	0.33	49.28	<u>⊢</u> •-	-
96.7	14.6	21	126.6	13.8	41	-29.90	-37.44	-22.36	50.72	⊢■	
		45			65	-19.45	-40.23	1.32			-
Z -1.84	P 0.0665		Heterog	eneitv: Tau	² = 206.70: Chi ² =	12.47. df= 1 (p=0.12): l2=	91.98%				<u> </u>
									-40	00 -20.00	0.00 10.00
										Favours MCI	Favour
MCI pati	ents		Healthy c	ontrols							
mean	SD	N	mean	SD	N				Weight		
111.9	16.1	24	127.0	15.5	24	-15.10	-24.04	4 -6.16	50.77		
110.1	17.7	21	135.6	17.6	41	-25.50	-34.7	9 -16.21	49.23	<u> </u>	
		45			65	-20.22	-30.4	1 -10.03		-	
z	Р	40									
-3.89	0.0001		Hetero	ogeneity: T	au²= 32.44; Chi	²=2.50, df= 1 (p=0.1139);	l²= 59.98%			-40.00 -20.00 0.00 Favours MCI	Favour
MCI patie	nt-		Haalthy cor	atrole							
wici patie	inco		fieatiny cor	101013							
mean 65.9		N24	mean 76.4						-	.	<u> </u>
00.0	13.1	24	/0.4	21.0	24	-10.50	-21.11	0.11	10.55		
71.0	16.7	21	77.8	16.7	41	-6.80	-15.58	1.98	83.67	⊢∎	<u>+</u>
		45			65	-7.40	-10.08	-4.72		-	
z	Ρ	45									
-5.41	0.0000		Heteroge	eneity: Tau	²= -17.85; Chi²=0).28, df= 1 (p=0.5985); l ² =	-2.61%		-25.0	10 -15.00 -5.00	5.00
										Favours MCI	Favour
MCI pati	ents		Healthy co	ontrols							
mean	SD	N	mean	SD	N	Mean Difference			Weight		
64.2	13.9	24	67.8	15.1	24	-3.60	-11.81	4.61	44.46		_
66.3	12.1	21	75.8	16.6	41	-9.50	-16.75	-2.25	55.54	- i	
					CF	<i></i>	12.52	1 1 2			
z	Ρ	45			65	-6.88	-12.62	-1.13			
	mean 89.3 85.8 86.0 Z -6.66 MCI patie mean 101.3 96.7 Z -1.84 MCI patie mean 111.9 110.1 Z -3.89 MCI patie mean 65.9 71.0 Z -5.41 MCI patie mean 65.9 71.0 Z -5.41 MCI patie mean 64.2	89.3 2.7 85.8 10.0 86.0 7.2 Z P -6.66 0.0000 MCI patients SD 101.3 15.2 96.7 14.6 Z P -1.84 0.0665 MCI patients mean MCI patients SD 111.9 16.1 110.1 17.7 Z P -3.89 0.0001 MCI patients mean mean SD 65.9 15.1 71.0 16.7 Z P -5.41 0.0000 MCI patients mean SD 15.1 71.0 16.7 Z P -5.41 0.0000 MCI patients mean mean SD 64.2 13.9	mean SD N 89.3 2.7 23 85.8 10.0 24 85.8 10.0 24 86.0 7.2 21 Z P 68 2.6.66 0.0000 1 MCI patients 21 mean SD N 101.3 15.2 24 96.7 14.6 21 Z P . 45 Z P . . MCI patients . . .	mean SD N mean 89.3 2.7 23 102.2 85.8 10.0 24 94.3 86.0 7.2 21 103.6 Z P 68 102.2 6.0 7.2 21 103.6 MCI patients Healthy co 101.3 15.2 24 110 96.7 14.6 21 126.6 110 101.3 15.2 24 110 96.7 14.6 21 126.6 126.6 126.6 126.6 MCI patients P 135.6 45 Healthy co 126.6 MCI patients SD N mean 127.0 135.6 110.1 17.7 21 135.6 127.0 135.6 Z P -3.89 0.00001 45 127.0 110.1 17.7 21 135.6 128.0 128.0 MCI patients P N Mean	mean SD N mean SD 89.3 2.7 23 102.2 1.8 85.8 10.0 24 94.3 11.3 86.0 7.2 21 103.6 8.9 68 - - 68 - MCI patients Healthy controls - 68 mean SD N mean SD 101.3 15.2 24 110 16.7 96.7 14.6 21 126.6 13.8 Z P -1.84 0.0665 Heterogeneity: Tau MCI patients Healthy controls - 15.5 110.1 17.7 21 135.6 17.6 111.9 16.1 24 127.0 15.5 110.1 17.7 21 135.6 17.6 MCI patients Healthy controls Healthy controls - mean SD N mean SD <	mean SD N mean SD N 89.3 2.7 23 102.2 1.8 15 85.8 10.0 24 94.3 11.3 24 86.0 7.2 21 103.6 8.9 41 68 80 7 2 103.6 8.9 41 68 80 7 2 103.6 8.9 41 68 80 7 24 103.6 8.9 41 68 80 7 80 7 7 7 7 MCI patients Healthy controls 101.3 15.2 24 110 16.7 24 96.7 14.6 21 126.6 13.8 41 10 111.9 16.1 24 127.0 15.5 24 10 110.1 17.7 21 135.6 17.6 41 10 110.1 17.7 21 13	mean SD N mean SD N Mean Difference 89.3 2.7 23 102.2 1.8 15 -12.90 85.8 10.0 24 94.3 11.3 24 -8.50 66.0 7.2 21 103.6 8.9 41 -17.60 7 68 80 -13.39 -13.39 -13.39 -13.39 7 66 90.000 Heterogeneity: Tau*= 8.34; Chi*=6.90, df= 2 (p=0.0318); P= -10.13 15.2 24 110 16.7 24 -8.70 MCI patients Healthy controls - - -19.45 -19.45 7 14.6 21 126.6 13.8 41 -29.90 7 14.6 21 126.6 13.8 41 -29.90 7 14.6 21 126.6 13.8 41 -29.90 111.3 16.1 24 127.0 15.5 24 -15.10 111.1	mean SD N mean SD N Mean Difference Q 9 89.3 2.7 23 102.2 1.8 15 -12.90 -14.33 85.8 10.0 24 94.3 11.3 24 -6.80 -14.54 86.0 7.2 21 103.6 8.9 41 -17.60 -21.71 68 - 9 41 -17.60 -21.71 -13.39 -17.34 2 P -66 0.0000 Heterogeneity: Tau'= 8.34; Chi=6.90, df= 2 (p=0.0318); P= 70.99% -17.73 MCl patients Healthy controls Healthy controls -17.73 96.7 14.6 21 126.6 13.8 41 -29.90 -37.44 2 P -18.4 0.0665 Heterogeneity: Tau'= 206.70; Chi'=12.47, df=1 (p=0.12); P= 91.98% -117.13 MCl patients Healthy controls Healthy controls -15.10 -24.00 110.1 17.7 21 135.6 17.6 41	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	mean 50 N mean 50 N Mean Difference C195 % Weight 88.8 100 24 94.3 11.3 2.4 4.5.0 -14.35 -1.1.4 45.57 * 85.8 100 2.4 94.3 11.3 2.4 -4.5.0 -14.3.4 -2.4.6 22.6.9 - * 85.0 7.2 21 103.6 8.9 41 -17.60 -21.71 -13.49 31.74 - * 7 p 68 80 -13.39 -17.34 -9.45 .

Fig 2. Forest plots of weighted mean difference (WMD) of MCI patients for the mean and each single quadrant RNFL. Horizontal lines are 95% confidence intervals.

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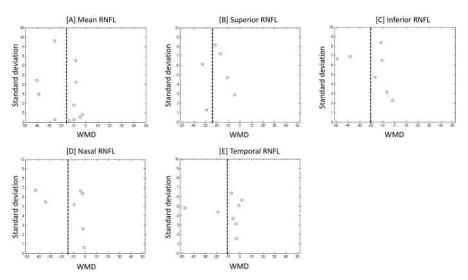


Fig 3. Funnel plots for evaluating the publication bias. Points indicate weighted mean difference (WMD) from studies included in meta—analysis of the mean [A], superior [B], inferior [C], nasal [D] and temporal [E] RNFL quadrants.

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pooled through the random effects model. The meta-analysis of these data showed that the mean RNFL thickness in MCI was reduced significantly compared with healthy controls (WMD = -13.39, 95% CI: -17.34 to -9.45, p = 0.031, Fig 2). Moreover meta-analysis of each quadrant data showed that there was, with the exception of the superior quadrant, an overall poor heterogeneity across studies: superior (I^2 = 91.98%), inferior (I^2 = 59.98%), nasal (I^2 = -2.61%), and temporal (I^2 = 10.25%). However, data showed significant thinner RNFL in the inferior (WMD = -20.22, 95% CI: -30.41 to -10.03, p = 0.0001), nasal (WMD = -7.4, 95% CI: -10.08 to -4.7, p = 0.0000), and temporal (WMD = -6.88, 95% CI: -12.62 to -1.13, p = 0.01), quadrants with the exception of the superior quadrant where RNFL just tent to be thinner respect to HC (WMD = -19.45, 95% CI: -40.23 to 1.32, p = 0.06). In summary, the results of meta-analysis showed that there was a significant RNFL thickness reduction in the mean and in single quadrants RNFL in MCI patients, with the notable exception of the superior quadrant.

Publication Bias

From the funnel plot analysis it appears that there is no correlation between study size and effect size or any other evidence of publication bias ($\underline{Fig 3}$).

Discussion

In this review, we performed a comprehensive meta-analysis investigating the role of OCT in detecting reduced RNFL thickness in AD patients. Since a transient phase may precede the full-blown clinical manifestation of AD, we examined the role of OCT also in sensing RNFL thickness changes in MCI. We found that the OCT is a well-suited paraclinical methodology to assess RNFL thickness in both AD and MCI disorders.

Despite many advances in the understanding of its pathophysiology, AD is still difficult to diagnose, chiefly because: a) diagnosis is mainly based on psychometric assessments by a multidisciplinary team (neurologists, psychiatrists, and psychologist), b) because physical and neurological examinations are not specific for this disorder, and c) because, brain physiological senescence processes may mask the subtle pathological neurodegenerative processes leading to AD. Because of inter- and intra-individual variability, neurophysiological and neuroimaging tests have not yet been considered as criteria on which to base a diagnosis. In fact, neurophysiological as well as other paraclinical tests are recommended only on suspicion of secondary causes of dementia as part of the differential diagnosis of AD. A confirmation of the AD diagnosis is possible only with *post mortem* histopathology. Nonetheless, the last few decades have seen the use of structural and functional techniques as potential biomarkers that might also identify factors that may predispose individuals to AD.

The OCT technique for measurement of the peripapillary RNFL, the macular thickness and volume, has been used as useful tool for the detection of significant retinal changes in patients and these measures roughly correlate with the severity of the disease.

Results from our meta-analysis based on 11 studies, suggested that AD patients are likely to have a reduced RNFL thickness as assessed by OCT. This reduction in RNFL thickness, as observed in most studies on AD patients, was significantly greater than that observed in the age-matched controls and thus cannot be exclusively ascribed to aging (see a synopsis of published OCT studies in AD in <u>Table 1</u>). Further meta-analysis showed a uniform significant decrease in RNFL thickness in each of the four retinal quadrants, suggesting that whatever factors cause the degenerative process in AD progression, affect the entire retinal layer.

Although little is known about the neurobiological basis of the physiological and structural changes that occur in the brain of AD patients, some histological and morpho-functional studies point to the concept that the same neurodegenerative processes, which affect the brain, may also affect the nerve fiber layer of the retina, as an integrated part of the nervous system.

In animal models, expressing mutant forms of amyloid precursors, and histological studies on post mortem human AD eyes, researchers have observed various retinal pathological changes, such as depletion of axons in the optic nerves and extensive retinal ganglion cell loss [20,21,50,51]. These changes were accompanied by accumulation within the retina and its microvasculature of toxic aminoacids classically described in the degenerative processes of AD, such as fibrillar tau and A β aggregates and specific signs of neuroinflammation [52–57].

In investigations using the optic nerve analyser, a higher proportion of AD patients than age-matched healthy subjects showed signs of optic neuropathy and this manifested as optic disc atrophy, pathologic optic disc cupping, and thinning of the neuroretinal rim and of the RNFL [58,59].

In agreement with post mortem studies, OCT data studies indicate a significant decline in peripapillary RNFL and changes in macular thickness and volume that is progressive from MCI to AD eyes. Parisi and colleagues first used OCT to study a group of AD patients and compared them with a group of age-matched controls. In AD patients, OCT results showed a reduced thickness of the retina NFL overall and in each quadrant examined they found involvement of the neuroretinal tissue in AD [31,32]. The mean RNFL thickness was confirmed to be reduced in AD patients by several independent groups [33–36]. Most studies observed a significant reduction of RNFL thickness in all quadrants [31,32,36,44], but predominantly in the superior [34,35,37,43,60] and inferior quadrants [34,37]. The retinal thinning in AD patients was confirmed despite the different commercially available OCT devices used [36,49].

OCT studies in AD patients showed RNFL thickness reduction that was directly proportional to abnormalities in pattern electroretinogram, reflecting neuronal degeneration in the retinal ganglion cell layer [31,32], not related to changes in cortical visual evoked responses, and hence probably not a consequence of retrograde degeneration [60]. Both positive [60,61] and absent [33,35,37,43,62] correlation was observed between the reduced total macular volume in patients with AD and the severity of the disease as assessed by the mini mental state examination questionnaire (MMSE) [60,61]. Unfortunately, it was not possible to make a subgroup analysis for this due to lack of power and high variability of the data.

OCT is be a useful tool for evaluating the progression of neurodegenerative processes that lead to AD. Based on 3 studies, our present meta-analysis showed a significant RNFL reduction in MCI patients as well compared with age-matched healthy controls. Ancillary quadrant meta-analysis in MCI revealed a significant reduction in RNFL thickness for each quadrant, especially in the inferior and nasal, with the exception of the superior, where the reduction only approached the significance level (p = 0.06). This lack of significance can be ascribed to the lack of statistical power due to small amount of patients enrolled. Further studies in a large cohort of patients are needed in order to clarify the exact degree of each quadrant involvement in MCI. Few studies compared MCI versus AD patients and healthy aged people. Kesler et al. [37] observed that the mean RNFL was significantly thinner in both AD and MCI patients groups compared to controls, and that the MCI group fell in between the other two groups. This difference was particularly prominent in the inferior quadrant, whereas AD patients had significantly thinner retinal NFL values also in the superior quadrant [37].

Finally, present meta-analysis cannot overcome certain limitations of the literature. First, the total number of patients is smaller than we would expect to generalize our results, although our cohort was sufficient to disclose strong statistical significance. Second, the variable assortment of OCT instruments (we counted 7 different apparatus) used across studies prevented us doing examination of whether differences in RNFL thickness were attributable to different types of OCT. The latter is of particular relevance for the reproducibility of OCT results in low compliance patients, considering, among all, the intrinsic between apparatus variability in centring procedure around the optic disc, eye tracking system, and in length of examination time.

Conclusions

Overall, the results of this meta-analysis showed that RNFL thickness decreased in all quadrants in AD patients. These findings strongly suggest that degeneration of retinal ganglion cells should be added to the constellation of neuropathologic changes found in patients with AD on the one hand, and that RNFL thickness can be used to distinguish AD patients from normal ageing, on the other. Moreover, the meta-analysis data also revealed that OCT can be useful to detect early RNFL abnormalities in MCI patients. Whether the subgroup of MCI patients with thinner RNFL have a higher annual incidence of conversion to AD [63] remains to be determined in an appropriately designed study. This is of particular interest in view of using OCT as a paraclinical test with prognostic value.

Future research in this subject area will surely provide a better assessment of the specificity of these OCT findings in AD, and their potential correlation with disease severity. We will see RNFL thickness measurements in patients with other dementias as an aid to diagnosis and we will see whether the RNFL can be used as a surrogate for magnetic resonance imaging (MRI) measurements of the brain.

Supporting Information

S1 Fig. PRISMA flow diagram of the search and study selection process. (TIFF)

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Author Contributions

Conceived and designed the experiments: CG VP. Performed the experiments: GC LZ. Analyzed the data: ADR FM AF. Contributed reagents/materials/analysis tools: ADR FM AF. Wrote the paper: GC VP GM PB AAS FP.

References

- 1. Blennow K, Leon MJD, Zetterberg H (2006) Alzheimer's disease. The Lancet 368: 387–403.
- Waring S, Rosenberg R (2008) Genome-wide association studies in Alzheimer disease. Arch Neurol. 65: 329–334. doi: <u>10.1001/archneur.65.3.329</u> PMID: <u>18332245</u>
- Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH et al. (2001) Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol. 58: 397–405. PMID: <u>11255443</u>
- Roberts R, Knopman D (2013) Classification and epidemiology of MCI. Clin Geriatr Med. 29: 753–772. doi: <u>10.1016/j.cger.2013.07.003</u> PMID: <u>24094295</u>
- Gainotti G, Quaranta D, Vita M, Marra C (2014) Neuropsychological predictors of conversion from mild cognitive impairment to Alzheimer's disease. J Alzheimers Dis. 38: 481–495. doi: <u>10.3233/JAD-130881</u> PMID: <u>24002185</u>
- Hutton J, Morris J, Elias J, Poston J (1993) Contrast sensitivity dysfunction in Alzheimer's disease. Neurology. 43: 2328–2330. PMID: <u>8232951</u>
- Gilmore G, Whitehouse P (1995) Contrast sensitivity in Alzheimer's disease: a 1-year longitudinal analysis. Optom Vis Sci. 72: 83–91. PMID: <u>7753532</u>
- Crow R, Levin L, LaBree L, Rubin R, Feldon S (2003) Sweep visual evoked potential evaluation of contrast sensitivity in Alzheimer's dementia. Invest Ophthalmol Vis Sci. 44: 875–878. PMID: <u>12556424</u>
- Gilmore G, Wenk H, Naylor L, Koss E (1994) Motion perception and Alzheimer's disease. J Gerontol. 49: P52–P57. PMID: <u>8126359</u>
- Rizzo M, Nawrot M (1998) Perception of movement and shape in Alzheimer's disease. Brain.: 2259– 2270. PMID: <u>9874479</u>
- Wijk H, Berg S, Sivik L, Steen B (1999) Colour discrimination, colour naming and colour preferences among individuals with Alzheimer's disease. Int J Geriatr Psychiatry. 14: 1000–1005. PMID: <u>10607966</u>
- Wijk H, Berg S, Bergman B, Hanson A, Sivik L, Steen B (2002) Colour perception among the very elderly related to visual and cognitive function. Scand J Caring Sci. 16: 91–102. PMID: <u>11985755</u>
- Salamone G, Di Lorenzo C, Mosti S, Lupo F, Cravello L, Palmer K et al. (2009) Color discrimination performance in patients with Alzheimer's disease. Dement Geriatr Cogn Disord. 27: 501–507. doi: <u>10.</u> <u>1159/000218366 PMID: 19451717</u>
- 14. Cogan D (1985) Visual disturbances with focal progressive dementing disease. Am J Ophthalmol. 100: 68–72. PMID: <u>3893141</u>
- Whitehouse P, Price D, Clark A, Coyle J, DeLong M (1981) Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. Ann Neurol. 10: 122–126. PMID: <u>7283399</u>
- van de Nes J, Nafe R, Schlote W (2008) Non-tau based neuronal degeneration in Alzheimer's disease —an immunocytochemical and quantitative study in the supragranular layers of the middle temporal neocortex. Brain Res. 1213: 152–165. doi: <u>10.1016/j.brainres.2008.03.043</u> PMID: <u>18455153</u>
- Leuba G, Kraftsik R (1994) Visual cortex in Alzheimer's disease: occurrence of neuronal death and glial proliferation, and correlation with pathological hallmarks. Neurobiol Aging. 15: 29–43. PMID: <u>8159261</u>
- Armstrong R (2005) Is there a spatial association between senile plaques and neurofibrillary tangles in Alzheimer's disease? Folia Neuropathol. 43: 133–138. PMID: <u>16245206</u>
- Sadun A, Borchert M, DeVita E, Hinton D, Bassi C (1987) Assessment of visual impairment in patients with Alzheimer's disease. Am J Ophthalmol. 104: 113–120. PMID: <u>3618708</u>
- Hinton D, Sadun A, Blanks J, Miller C (1986) Optic-nerve degeneration in Alzheimer's disease. N Engl J Med. 315: 485–487. PMID: <u>3736630</u>
- 21. Sadun A, Bassi C (1990) Optic nerve damage in Alzheimer's disease. Ophthalmology. 97: 9–17. PMID: 2314849
- Löffler K, Edward D, Tso M (1995) Immunoreactivity against tau, amyloid precursor protein, and betaamyloid in the human retina. Invest Ophthalmol Vis Sci. 36: 24–31. PMID: 7822152
- Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W et al. (1991) Optical coherence tomography. Science. 254: 1178–1181. PMID: <u>1957169</u>

- Puliafito CA, Hee MR, Lin CP, Reichel E, Schuman JS, Duker JS et al. (1995) Imaging of macular diseases with optical coherence tomography. Ophthalmology. 102: 217–229. PMID: <u>7862410</u>
- Schuman JS, Hee MR, Puliafito CA, Wong C, Pedut-Kloizman T, Lin CP et al. (1995) Quantification of nerve fiber layer thickness in normal and glaucomatous eyes using optical coherence tomography. Arch Ophthalmol. 113: 586–596. PMID: <u>7748128</u>
- Parisi V, Manni G, Gandolfi SA, Centofanti M, Colacino G, Bucci MG (1999) Visual function correlates with nerve fiber layer thickness in eyes affected by ocular hypertension. Invest Ophthalmol Vis Sci 40: 1828–1833. PMID: <u>10393056</u>
- Parisi V, Manni G, Spadaro M, Colacino G, Restuccia R, Marchi S et al. (1999) Correlation between morphological and functional retinal impairment in multiple sclerosis patients. Invest Ophthalmol Vis Sci. 40: 2520–2527. PMID: <u>10509645</u>
- Parisi V, Manni G, Centofanti M, Gandolfi SA, Olzi D, Bucci MG (2001) Correlation between optical coherence tomography, pattern electroretinogram, and visual evoked potentials in open-angle glaucoma patients. Ophthalmology 108: 905–912. PMID: <u>11320021</u>
- Parisi V, Pierelli F, Coppola G, Restuccia R, Ferrazzoli D, Scassa C et al. (2007) Reduction of optic nerve fiber layer thickness in CADASIL. Eur J Neurol 14: 627–631. PMID: <u>17539939</u>
- Kardon R (2011) Role of the macular optical coherence tomography scan in neuro-ophthalmology. J Neuroophthalmol. 31: 353–361. PMID: <u>22089499</u>
- Parisi V, Restuccia R, Fattapposta F, Mina C, Bucci MG, Pierelli F (2001) Morphological and functional retinal impairment in Alzheimer's disease patients. Clin Neurophysiol. 112: 1860–1867. PMID: <u>11595144</u>
- Parisi V (2003) Correlation between morphological and functional retinal impairment in patients affected by ocular hypertension, glaucoma, demyelinating optic neuritis and Alzheimer's disease. Semin Ophthalmol. 18: 50–57. PMID: 14566623
- Paquet C, Boissonnot M, Roger F, Dighiero P, Gil R, Hugon J (2007) Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Neurosci Lett. 420: 97–99. PMID: 17543991
- Lu Y, Li Z, Zhang X, Ming B, Jia J, Wang R et al. (2010) Retinal nerve fiber layer structure abnormalities in early Alzheimer's disease: evidence in optical coherence tomography. Neurosci Lett. 480: 69–72. doi: 10.1016/j.neulet.2010.06.006 PMID: 20609426
- Kirbas S, Turkyilmaz K, Anlar O, Tufekci A, Durmus M (2013) Retinal nerve fiber layer thickness in patients with Alzheimer disease. J Neuroophthalmol. 33: 58–61. PMID: <u>22918296</u>
- Marziani E, Pomati S, Ramolfo P, Cigada M, Giani A, Mariani C et al. (2013) Evaluation of retinal nerve fiber layer and ganglion cell layer thickness in Alzheimer's disease using spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 54: 5953–5958. doi: <u>10.1167/iovs.13-12046</u> PMID: <u>23920375</u>
- Kesler A, Vakhapova V, Korczyn A, Naftaliev E, Neudorfer M (2011) Retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Clin Neurol Neurosurg. 113: 523–526. doi: <u>10.</u> <u>1016/j.clineuro.2011.02.014</u> PMID: <u>21454010</u>
- Mahmoudian M, Ebrahimi S, Kiani Z (2009) An image processing technique for diagnosis of Alzheimer's disease. J Res Med Sci. 14: 205–209. PMID: <u>21772885</u>
- Tian T, Zhang B, Jia Y, Li Z (2014) Promise and challenge: the lens model as a biomarker for early diagnosis of Alzheimer's disease. Dis Markers. 2014: 826503. doi: <u>10.1155/2014/826503</u> PMID: <u>24688166</u>
- 40. Shen Y, Shi Z, Jia R, Zhu Y, Cheng Y, Feng W et al. (2013) The attenuation of retinal nerve fiber layer thickness and cognitive deterioration. Front Cell Neurosci. 7: 142. doi: <u>10.3389/fncel.2013.00142</u> PMID: <u>24065883</u>
- Shen Y, Liu L, Cheng Y, Feng W, Shi Z, Zhu Y et al. (2014) Retinal nerve fiber layer thickness is associated with episodic memory deficit in mild cognitive impairment patients. Curr Alzheimer Res. 11: 259–266. PMID: 24484274
- Shi Z, Wu Y, Wang M, Cao J, Feng W, Cheng Y et al. (2014) Greater attenuation of retinal nerve fiber layer thickness in Alzheimer's disease patients. J Alzheimers Dis. 40: 277–283. doi: <u>10.3233/JAD-131898</u> PMID: <u>24413621</u>
- Kromer R, Serbecic N, Hausner L, Froelich L, Aboul-Enein F, Beutelspacher SC (2014) Detection of Retinal Nerve Fiber Layer Defects in Alzheimer's Disease Using SD-OCT. Front Psychiatry. 5: 22. doi: 10.3389/fpsyt.2014.00022 PMID: 24616709
- Ascaso F, Cruz N, Modrego P, Lopez-Anton R, Santabárbara J, Pascual LF et al. (2014) Retinal alterations in mild cognitive impairment and Alzheimer's disease: an optical coherence tomography study. J Neurol. 261: 1522–1530. doi: <u>10.1007/s00415-014-7374-z</u> PMID: <u>24846203</u>

- **45.** Yu J, Feng Y, Xiang Y, Huang J, Savini G, Parisi V et al. (2014) Retinal nerve fiber layer thickness changes in Parkinson disease: a meta-analysis. PLoS One. 9: 10.
- **46.** Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis JP et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6: 10.
- Higgins J, Thompson S, Deeks J, Altman D (2003) Measuring inconsistency in meta-analyses. BMJ. 327: 557–560. PMID: <u>12958120</u>
- Egger M, Davey S, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ. 315: 629–634. PMID: <u>9310563</u>
- 49. Larrosa JM, Garcia-Martin E, Bambo MP, Pinilla J, Polo V, Otin S et al. (2014) Potential new diagnostic tool for Alzheimer's disease using a linear discriminant function for Fourier domain optical coherence tomography. Invest Ophthalmol Vis Sci. 55: 3043–3051. doi: <u>10.1167/iovs.13-13629</u> PMID: <u>24736054</u>
- Blanks J, Torigoe Y, Hinton D, Blanks R (1996) Retinal pathology in Alzheimer's disease. I. Ganglion cell loss in foveal/parafoveal retina. Neurobiol Aging. 17: 377–384. PMID: <u>8725899</u>
- Blanks JC, Schmidt SY, Torigoe Y, Porrello KV, Hinton DR, Blanks RH (1996) Retinal pathology in Alzheimer's disease. II. Regional neuron loss and glial changes in GCL. Neurobiol Aging 17: 385–395. PMID: 8725900
- Ning A, Cui J, To E, Ashe K, Matsubara J (2008) Amyloid-beta deposits lead to retinal degeneration in a mouse model of Alzheimer disease. Invest Ophthalmol Vis Sci. 49: 5136–5143. doi: <u>10.1167/iovs.08-1849</u> PMID: <u>18566467</u>
- Perez S, Lumayag S, Kovacs B, Mufson E, Xu S (2009) Beta-amyloid deposition and functional impairment in the retina of the APPswe/PS1DeltaE9 transgenic mouse model of Alzheimer's disease. Invest Ophthalmol Vis Sci. 50: 793–800. doi: 10.1167/iovs.08-2384 PMID: 18791173
- 54. Koronyo-Hamaoui M, Koronyo Y, Ljubimov A, Miller CA, Ko MK, Black KL et al. (2011) Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. Neuroimage. 1: S204–S217.
- 55. Liu B, Rasool S, Yang Z, Glabe CG, Schreiber SS, Ge J et al. (2009) Amyloid-peptide vaccinations reduce {beta}-amyloid plaques but exacerbate vascular deposition and inflammation in the retina of Alzheimer's transgenic mice. Am J Pathol. 175: 2099–2110. doi: <u>10.2353/ajpath.2009.090159</u> PMID: <u>19834067</u>
- Schön C, Hoffmann NA, Ochs SM, Burgold S, Filser S, Steinbach S et al. (2012) Long-term in vivo imaging of fibrillar tau in the retina of P301S transgenic mice. PLoS One. 7: 10.
- 57. Cohen RM, Rezai-Zadeh K, Weitz TM, Rentsendorj A, Gate D, Spivak I et al. (2013) A transgenic Alzheimer rat with plaques, tau pathology, behavioral impairment, oligomeric aβ, and frank neuronal loss. J Neurosci. 33: 6245–6256. doi: 10.1523/JNEUROSCI.3672-12.2013 PMID: 23575824
- Tsai CS, Ritch R, Schwartz B, Lee SS, Miller NR, Chi T et al. (1991) Optic nerve head and nerve fiber layer in Alzheimer's disease. Arch Ophthalmol. 109: 199–204. PMID: <u>1993028</u>
- Hedges TR 3rd, Perez Galves R, Speigelman D, Barbas NR, Peli E, Yardley CJ (1996) Retinal nerve fiber layer abnormalities in Alzheimer's disease. Acta Ophthalmol Scand. 74: 271–275. PMID: 8828725
- Iseri P, Altinaş O, Tokay T, Yüksel N (2006) Relationship between cognitive impairment and retinal morphological and visual functional abnormalities in Alzheimer disease. J Neuroophthalmol. 26: 18–24. PMID: 16518161
- Moreno-Ramos T, Benito-León J, Villarejo A, Bermejo-Pareja F (2013) Retinal nerve fiber layer thinning in dementia associated with Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease. J Alzheimers Dis. 34: 659–664. doi: 10.3233/JAD-121975 PMID: 23271313
- Kromer R, Serbecic N, Hausner L, Froelich L, Beutelspacher S (2013) Comparison of visual evoked potentials and retinal nerve fiber layer thickness in Alzheimer's disease. Front Neurol. 4: 203. doi: <u>10.</u> <u>3389/fneur.2013.00203</u> PMID: <u>24379800</u>
- Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO et al. (2004) Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 256: 240–246. PMID: <u>15324367</u>
- Berisha F, Feke G, Trempe C, McMeel J, Schepens C (2007) Retinal abnormalities in early Alzheimer's disease. Invest Ophthalmol Vis Sci. 48: 2285–2289. PMID: <u>17460292</u>