Correlation of OCTA and Volumetric MRI in Mild Cognitive Impairment and Alzheimer's Disease

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BACKGROUD AND OBJECTIVE: To evaluate the relationship between retinal microvascular parameters on optical coherence tomography angiography (OCTA) and neurodegenerative changes assessed by measurement of brain volume on volumetric magnetic resonance imaging (MRI) in Alzheimer's disease (AD) and mild cognitive impairment (MCI).

PATIENTS AND METHODS: Sixteen subjects with AD and MCI underwent OCTA imaging (3 mm x 3 mm and 6 mm x 6 mm scans) and volumetric brain MRI imaging with automated volumetric segmentation and quantification. Spearman's correlation (ρ) was performed between forebrain parenchyma, cortical gray matter, inferolateral ventricle (ILV), lateral ventricle (LV), and hippocampus (HP) MRI volumes and vessel density (VD), along with perfusion density (PD) for the 6-mm circle, 6-mm ring, 3-mm circle, and 3-mm ring Early Treatment Diabetic Retinopathy Study regions of the superficial capillary plexus.

RESULTS: Thirty eyes of 16 patients (seven MCI and nine AD) with good-quality OCTA images were analyzed. ILV volume inversely correlated with the VD in the 6-mm circle ($\rho = -0.565$, $P = .028$) and 3-mm ring ($\rho = -0.569$, $P = .027$) and PD in the 3-mm ring ($\rho = -0.605$, $P = .0169$). Forebrain, cortical gray matter, LV, and HP volumes did not significantly correlate with either VD or PD ($P > .05$).

CONCLUSIONS: In this pilot investigation, the authors found a significant correlation between reduction in the superficial capillary plexus VD and PD on OCTA and expansion of the ILV in MCI and AD. This relationship between the retinal microvasculature and cerebral volumetric changes deserves further investigation.

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INTRODUCTION

The spectrum of neurodegenerative pathologies in the aging brain includes Alzheimer's disease (AD), a progressive disease characterized by deposition of amyloid beta plaques and neurofibrillary tangles resulting in atrophy and vascular damage of the brain,[1,2] and mild cognitive impairment (MCI), a transitional stage between normal cognitive aging and dementia.[3] Brain tissue atrophy measured on volumetric magnetic resonance imaging (MRI) scans provides an objective and quantitative method to examine some of the neuropathological changes associated with both MCI and AD.[1]

MRI changes, such as atrophy of the brain and consequential ventricular enlargement, correlate with tau deposition and neuropsychological deficits in AD.[3,4] Ventriculomegaly is commonly observed in most neurodegenerative disorders and results from passive enlargement of the lateral, third, and fourth ventricles following brain parenchymal shrinkage. Significant ventricular enlargement has been associated with AD.[3-5] In the retina, it is widely recognized that there is reduction of retinal nerve fiber layer (RNFL) thickness, ganglion cell-inner plexiform layer (GC-IPL) thickness, and total macular thickness in AD.[6,7,8] There is also evidence that these structural retinal thickness changes

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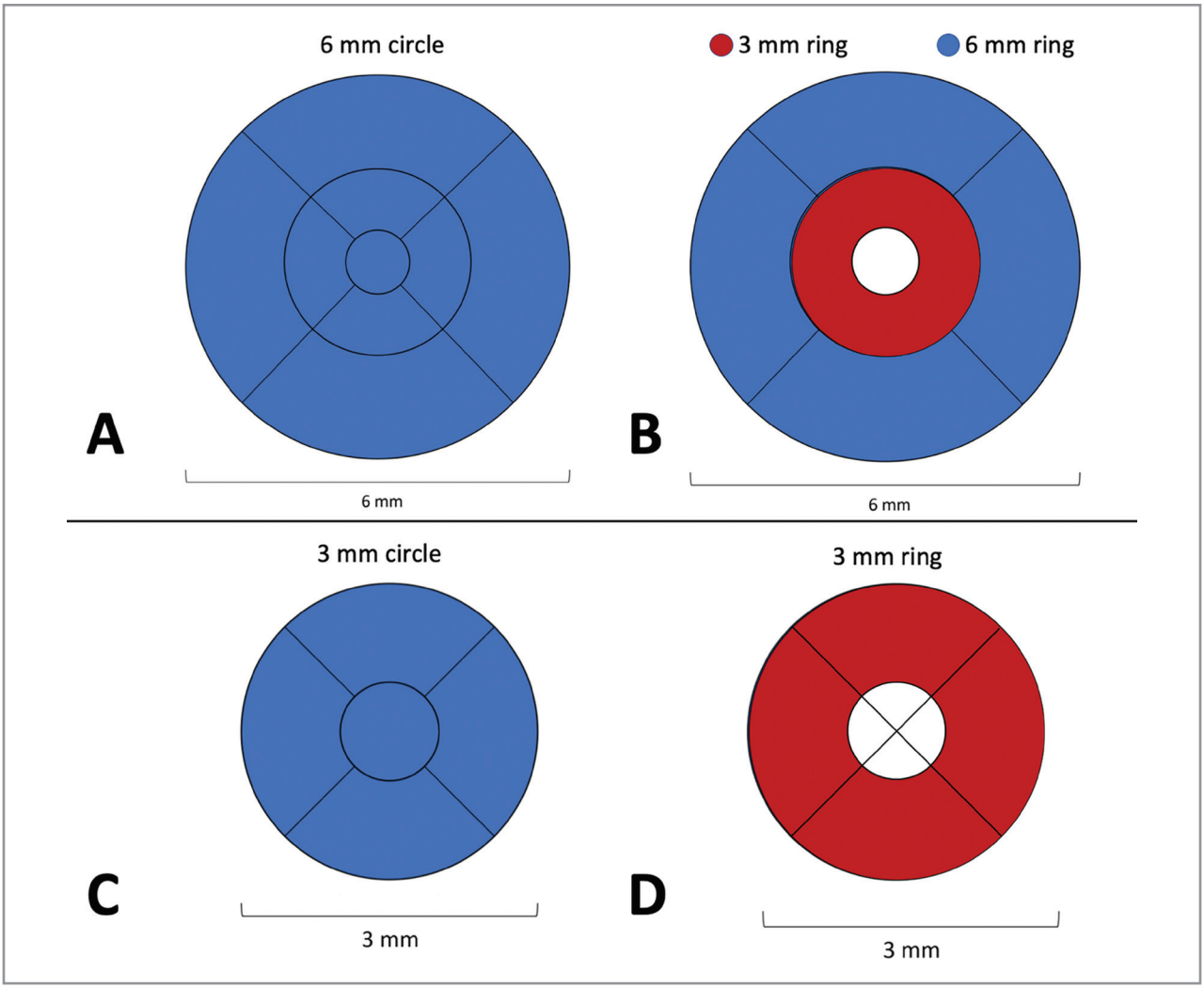

Figure 1. Diagram showing the Early Treatment Diabetic Retinopathy Study grid region overlay used for calculation of the vessel density (VD) and perfusion density (PD) in the different regions. (A) Representation of a 6 mm x 6 mm optical coherence tomography angiography (OCTA) scan with the area in blue representing the 6-mm circle. (B). Representation of a 6 mm x 6 mm OCTA scan with the area in blue representing the 6-mm ring and the area in red representing the 3-mm ring. (C). Representation of a 3 mm x 3 mm OCTA scan with the area in blue representing the 3-mm circle. (D). Representation of a 3 mm x 3 mm OCTA scan with the area in red representing the 3-mm ring. VD and PD values for each respective region were calculated by averaging values over the highlighted areas.

correlate with MRI volumes.[9,10] More recently, optical coherence tomography angiography (OCTA) has also been shown to be capable of detecting neurodegenerative vascular changes in the retina measured by a reduction in retinal vascular density in AD and MCI as well as potentially in preclinical AD.[6,11,12]

These retinal microvascular changes may mirror changes in the cerebral microvasculature in AD and MCI due to their anatomical, embryological, and physiological homology.[13] Although it is challenging to directly visualize and quantify the cerebral microvasculature, brain volumes can be quantified more readily and used as a surrogate. Automated software for volumetric measurements on brain MRI may reduce rater-dependent bias and may make these structural measures more sensitive for detecting brain atrophy.[14]

In this investigation, we hypothesized that retinal microvascular loss detected by OCTA may correlate with changes in brain volume quantified by either structural atrophy or ventricular expansion on automated volumetric MRI in AD and MCI.

PATIENTS AND METHODS

Participants and Protocol

Our research protocol was approved by the Institutional Review Board for Human Research of Duke University in Durham, NC. Written informed

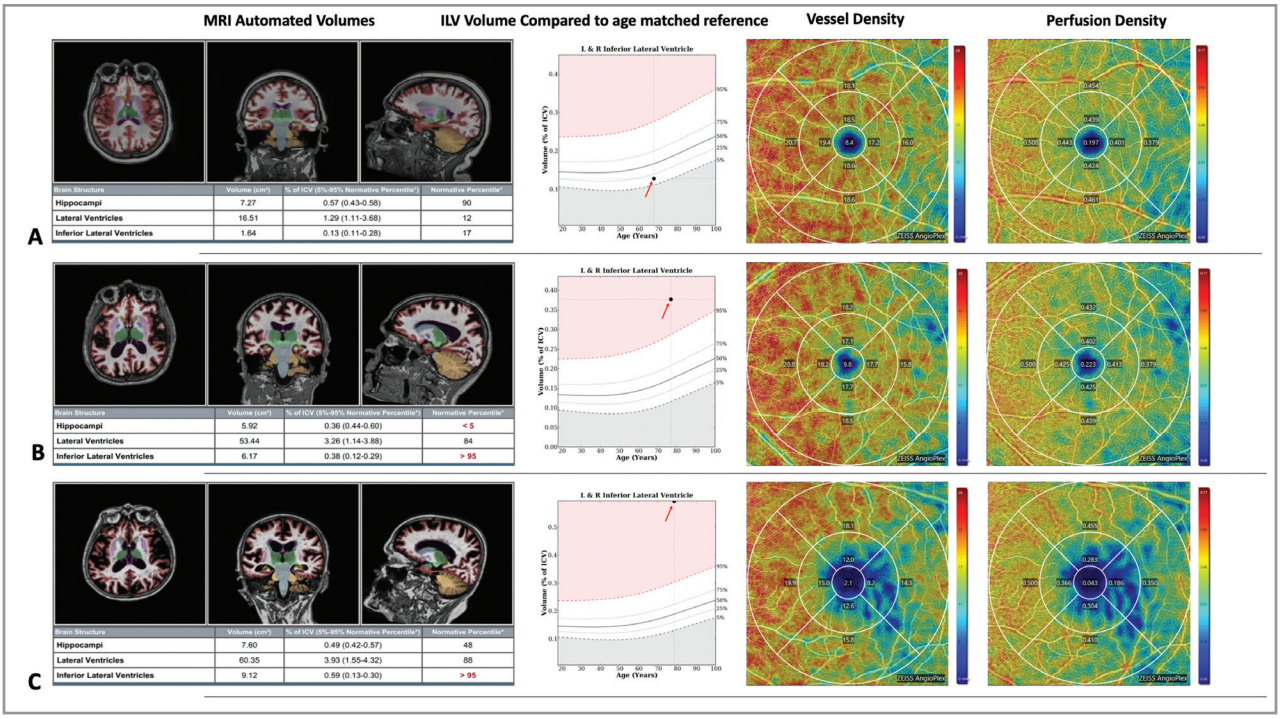

Figure 2. Volumetric magnetic resonance imaging (MRI) images (left column, with NeuroQuant software normalized brain volumes by quantifying percentage of total intracranial volume and comparison to age-matched reference values provided below the MRI images) and corresponding 6 mm x 6 mm optical coherence tomography angiography (OCTA) images of the superficial capillary plexus showing vessel density (VD) maps and perfusion density (PD) maps of the left eye of three participants with varying degree of severity of neurodegenerative changes and dementia. Scale on the right of the maps shows red indicating preserved VD and PD and blue indicating loss of VD and PD. (A) A 71-year-old female with mild cognitive impairment (MCI) and a Mini-Mental State Exam (MMSE) score of 28. The inferolateral ventricular (ILV) volume is 1.64 cm^2, which is at the 17th percentile of an age-matched reference. (B) An 80-year-old male with Alzheimer's disease (AD) and a MMSE of 21. There is expansion of the ILV to 6.17 cm^2, which is greater than the 95th normative percentile, and there is moderate reduction in both VD and PD. (C) An 80-year-old with AD and MMSE score of 16 with expansion of ILV to 9.12 cm^2 that is significantly greater than the 95th normative percentile, and there is corresponding severe reduction in both VD and PD.

consent was obtained prior to enrollment from all participants or their designated medical power of attorney in those with severe cognitive impairment. The study followed the tenets of the Declaration of Helsinki.

In this cross-sectional study (NCT03233646), AD and MCI subjects aged 50 years and older were enrolled at the Duke Memory Disorders Clinic. Exclusion criteria included a history of non-AD associated dementia, diabetes mellitus, uncontrolled hypertension, demyelinating disorders, glaucoma, age-related macular degeneration, intraocular surgery other than uncomplicated cataract extraction, retinal pathology that could interfere with OCTA analysis, or corrected visual acuity worse than 20/40. AD and MCI subjects were evaluated and clinically diagnosed by an experienced neurologist (JRB) based on recommendations by the National Institute on Aging-Alzheimer's Association for diagnostic guidelines.[15] Clinical history, cognitive testing, laboratory values, and imaging were reviewed for diagnostic accuracy by an experienced neurologist with a specialization in memory disorders (JRB).

Optical Coherence Tomography Angiography Image Acquisition

All subjects were imaged using a spectral-domain OCTA machine (Cirrus HD-5000 AngioPlex; Carl Zeiss Meditec, Dublin, CA) with a scan rate of 68,000 A-scans per second. Both 3 mm x 3 mm and 6 mm x 6 mm images centered on the fovea were acquired. OCTA images that were poor quality (less than 7/10 signal strength) or had low resolution, uncorrectable segmentation errors, projection artifact, or motion artifact were excluded. Segmentation of full-thickness retinal scans in the superficial capillary plexus (SCP) was automated using OCTA software (Version 10.0;

TABLE 1

Demographics and Clinical Characteristics of Subjects With MCI and AD

	MCI (n = 7)	AD (n = 9)	Average (n = 16)
Age (Years)	70.7 ± 9.1	75.2 ± 7.5	73.3 ± 8.3
Female Gender % (n)	42.9% (n = 3/7)	55.5% (n = 5/9)	50% (n = 8/16)
Years of Education	15.0 ± 2.4	16.4 ± 1.9	15.8 ± 2.2
Mini-Mental State Exam Score	26.0 ± 1.4	21.6 ± 3.0	23.5 ± 3.3

MCI = mild cognitive impairment; AD = Alzheimer's disease

TABLE 2

OCT and OCTA Parameters for Subjects With AD and MCI

Parameter	MCI	AD	Average
OCT parameters			
Average CST (μm)	261.44 ± 17.42 (n = 6)	268.86 ± 33.38 (n = 9)	264.5 ± 24.9 (n = 15)
Average RNFL thickness (μm)	85 ± 6.94 (n = 6)	87.38 ± 7.85 (n = 9)	117.62 ± 65.88 (n = 15)
Average GC-IPL thickness (μm)	74.63 ± 7.08 (n = 7)	77.21 ± 6.13 (n = 9)	75.76 ± 6.60 (n = 16)
OCTA parameters			
FAZ area (mm^2), 3 mm x 3mm	0.17 ± 0.05 (n = 7)	0.17 ± 0.10 (n = 9)	0.17 ± 0.07 (n = 16)
OCTA perfusion density			
6-mm circle, 6 mm x 6 mm	0.44 ± 0.03 (n = 6)	0.45 ± 0.01 (n = 9)	0.44 ± 0.02 (n = 15)
3-mm ring, 6 mm x 6 mm	0.42 ± 0.04 (n = 6)	0.43 ± 0.03 (n = 9)	0.43 ± 0.04 (n = 15)
6-mm ring, 6 mm x 6 mm	0.45 ± 0.02 (n = 6)	0.46 ± 0.01 (n = 9)	0.45 ± 0.02 (n = 15)
3-mm circle, 3 mm x 3 mm	0.35 ± 0.04 (n = 7)	0.38 ± 0.01 (n = 9)	0.36 ± 0.04 (n = 16)
3-mm ring, 3 mm x 3 mm	0.36 ± 0.04 (n = 7)	0.40 ± 0.01 (n = 9)	0.38 ± 0.04 (n = 16)
OCTA vessel density (/mm)			
6-mm circle, 6 mm x 6 mm	17.77 ± 1.18 (n = 6)	18.31 ± 0.52 (n = 9)	17.98 ± 0.99 (n = 15)
3-mm ring, 6 mm x 6 mm	17.57 ± 1.83 (n = 6)	18.10 ± 1.29 (n = 9)	17.78 ± 1.60 (n = 15)
6-mm ring, 6 mm x 6 mm	18.07 ± 1.01 (n = 6)	18.63 ± 0.55 (n = 9)	18.29 ± 0.88 (n = 15)
3-mm circle, 3 mm x 3 mm	18.96 ± 2.70 (n = 7)	21.28 ± 0.65 (n = 9)	19.98 ± 2.33 (n = 16)
3-mm ring, 3 mm x 3 mm	19.87 ± 2.58 (n = 7)	22.23 ± 0.58 (n = 9)	20.90 ± 2.27 (n = 16)

OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; AD = Alzheimer's disease; MCI = mild cognitive impairment; CST = central subfield thickness; RNFL = retinal nerve fiber layer; GC-IPL = ganglion cell-inner plexiform layer; PD = perfusion density; VD = vessel density; FAZ = foveal avascular zone

Carl Zeiss Meditec, Dublin, CA). The superficial capillary plexus was calculated with the inner surface being the internal limiting membrane (ILM) and the outer surface being an approximation of the inner plexiform layer (IPL), which was estimated by the following equation: ZIPL = ZILM+70%*(TILM-OPL), where ZIPL is the boundary location of the estimated IPL, ZILM is the boundary location of the ILM, and TILM-OPL is the thickness between ILM and the outer plexiform layer (OPL). The software automatically quantified the average vessel density (VD) and perfusion density (PD) for the 3 mm x 3 mm and 6 mm x 6 mm SCP images over the central macula using an Early Treatment Diabetic Retinopathy Study (ETDRS) grid overlay. VD was defined as the total length of perfused vasculature per unit area (units: inverse millimeter), and PD was defined as the total area of perfused vasculature per unit area in the region of

TABLE 3

Automated Volumetric Brain MRI Parameters for Subjects With AD and MCI

Parameter (cm^2)	MCI (n=7)	AD (n=9)	Total (n=16)
Hippocampal volume	6.43 ± 0.87	7.00 ± 1.18	6.68 ± 1.02
Lateral ventricle volume	47.39 ± 22.31	37.18 ± 19.03	42.93 ± 20.92
Inferior lateral ventricle volume	4.40 ± 2.35	2.62 ± 1.20	3.62 ± 2.09
Forebrain parenchyma LH volume	455.79 ± 27.20	468.91 ± 43.83	461.53 ± 34.76
Forebrain parenchyma RH volume	456.67 ± 29.50	482.23 ± 45.23	467.85 ± 38.13
Cortical gray matter LH volume	214.21 ± 16.20	219.55 ± 28.65	216.55 ± 21.81
Cortical gray matter RH volume	213.23 ± 18.97	224.80 ± 30.03	218.29 ± 24.24
Lateral ventricle LH volume	22.85 ± 11.68	19.20 ± 10.35	21.25 ± 10.91
Lateral ventricle RH volume	24.55 ± 11.34	17.98 ± 8.90	21.67 ± 10.56
Inferior lateral ventricle LH volume	2.00 ± 0.86	1.39 ± 0.65	1.73 ± 0.81
Inferior lateral ventricle RH volume	2.40 ± 1.51	1.23 ± 0.62	1.89 ± 1.32
Hippocampus LH volume	3.13 ± 0.42	3.37 ± 0.66	3.24 ± 0.53
Hippocampus RH volume	3.30 ± 0.53	3.63 ± 0.53	3.44 ± 0.54

MRI = magnetic resonance imaging; AD = Alzheimer's disease; MCI = mild cognitive impairment; LH = left hemisphere; RH = right hemisphere

measurement (unitless). The VD and PD were automatically calculated for the 3-mm circle and 3-mm ring regions of 3 mm x 3 mm OCTA images and for 6-mm circle, 6-mm ring, and 3-mm ring regions of 6 mm x 6 mm OCTA images (Figure 1). The foveal avascular zone (FAZ) area was automatically segmented and quantified using the OCTA software. The automated segmentation boundaries of the FAZ area were manually verified for accuracy (SPY).

In addition, 512 x 128 macular cube and 200 x 200 optic disc cube scans were captured. OCT images with poor quality (less than 7/10) or motion artifacts were excluded. Central subfield thickness (CST), GC-IPL thickness (over the 14.13 mm^2 elliptical annulus area centered on the fovea), and average RNFL thickness (using a 3.46-mm diameter circle centered on the optic disc) were recorded.

Volumetric MRI

All subjects underwent noncontrast brain MRI at 3 Tesla. Images were processed using NeuroQuant (NQ, version 1; CorTechs Labs, San Diego, CA), which is an automated image analysis software program.[13] Volume morphometry reports were available for 11 regional brain structures, including three regions of interest particularly helpful in the evaluation of neurodementia: the inferolateral ventricle (ILV), lateral ventricle (LV), and hippocampus (HP) along with the forebrain parenchyma and cortical gray matter volumes. For each region of interest, age-related atrophy reports were generated comparing subjects' MRI volumetric results to gender- and age-matched reference distributions. Total volume (cm^3) for each brain structure was used in the analysis.

Statistical Analysis

If measurements were available in both eyes, the average parameter estimate was calculated. Ordinary least squares regression analysis and Spearman's correlation (ρ) were performed to explore the relationship between each of the vessel density or perfusion density SCP parameters in the central 6 mm x 6 mm or 3 mm x 3 mm circles and each of the three MRI volume parameters of interest. Due to the exploratory nature of this pilot study, no adjustment was made for multiple comparisons.

RESULTS

A total of 32 eyes from 16 patients (nine AD and seven MCI) were enrolled. Two eyes, one each from an AD and MCI subject, were excluded due to poor OCTA image quality. A total of 30 eyes from nine AD and seven MCI patients were analyzed. In addition, average GC-IPL thickness and VD and PD for 6 mm × 6 mm OCTA measurements were not available for one eye of one MCI subject.

The mean age was 75.2 years ± 7.5 years for the AD group and 70.7 years ± 9.1 years for the MCI group. The AD group had 55.5% females (n = 5/9) and the MCI group had 42.9% females (n = 3/7). Both groups

TABLE 4

Spearman Correlation Coefficients of OCTA and Volumetric Brain MRI Parameters for Subjects With AD and MCI

Parameter	Spearman ρ	*P* Value
Hippocampal volume		
Average CST	0.087	.75
Average RNFL thickness	0.295	.29
Average GC-IPL thickness	0.4256	.10
FAZ area, 3 mm x 3 mm	-0.0811	.77
Perfusion density		
6-mm circle, 6 mm x 6 mm	-0.0376	.89
3-mm ring, 6 mm x 6 mm	0.0143	.96
6-mm ring, 6 mm x 6 mm	-0.0894	.75
3-mm circle, 6 mm x 6 mm	-0.2046	.45
3-mm ring, 6 mm x 6 mm	-0.2399	.37
Vessel density		
6-mm circle, 6 mm x 6 mm	0.0357	.89
3-mm ring, 6 mm x 6 mm	-0.0286	.92
6-mm ring, 6 mm x 6 mm	0.1609	.57
3-mm circle, 3 mm x 3 mm	-0.0824	.76
3-mm ring, 3 mm x 3 mm	-0.0824	.76
Lateral ventricle volume		
Average CST	0.139	.61
Average RNFL thickness	0.147	.60
Average GC-IPL thickness	0.3387	.19
FAZ area, 3 mm x 3 mm	-0.4270	.11
Perfusion density		
6-mm circle, 6 mm x 6 mm	-0.2543	.36
3-mm ring, 6 mm x 6 mm	-0.4719	.076
6-mm ring, 6 mm x 6 mm	-0.2431	.38
3-mm circle, 3 mm x 3 mm	0.0942	.73
3-mm ring, 3 mm x 3 mm	-0.0883	.75
Vessel density		
6-mm circle, 6 mm x 6 mm	-0.4075	.13
3-mm ring, 6 mm x 6 mm	-0.4361	.10
6-mm ring, 6 mm x 6 mm	-0.3861	.16
3-mm circle, 3 mm x 3 mm	0.0382	.89
3-mm ring, 3 mm x 3 mm	-0.1471	.59
Inferior lateral ventricle volume		
Average CST	-0.043	.88
Average RNFL thickness	0.098	.73
Average GC-IPL thickness	0.2277	.396
FAZ area, 3 mm x 3 mm	-0.4626	.08
Perfusion density		
6-mm circle, 6 mm x 6 mm	-0.4597	.085

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3-mm ring, 6 mm x 6 mm	-0.6047	.0169*
6-mm ring, 6 mm x 6 mm	-0.4007	.14
3-mm circle, 3 mm x 3 mm	-0.0766	.78
3mm ring, 3 mm x 3 mm	-0.2239	.41
Vessel density		
6-mm circle, 6 mm x 6 mm	-0.5653	.0281*
3-mm ring, 6 mm x 6 mm	-0.5689	.0269*
6-mm ring, 6 mm x 6 mm	-0.4204	.12
3-mm circle, 3 mm x 3 mm	-0.1795	.51
3-mm ring, 3 mm x 3 mm	-0.3385	.19
Forebrain parenchyma volume		
Average CST	0.286	.28
Average RNFL thickness	0.369	.18
Average GC-IPL thickness	0.049	.86
FAZ area, 3 mm x 3 mm	-0.05	.86
Perfusion density		
6-mm circle, 6 mm x 6 mm	0.507	.054
3-mm ring, 6 mm x 6 mm	0.375	.17
6-mm ring, 6 mm x 6 mm	0.440	.10
3-mm circle, 3 mm x 3 mm	0.330	.21
3-mm ring, 3 mm x 3 mm	0.338	.22
Vessel density		
6-mm circle, 6 mm x 6 mm	0.422	.12
3-mm ring, 6 mm x 6 mm	0.393	.15
6-mm ring, 6 mm x 6 mm	0.343	.21
3-mm circle, 3 mm x 3 mm	0.297	.26
3-mm ring, 3 mm x 3 mm	0.279	.29
Cortical gray matter volume		
Average CST	0.358	.17
Average RNFL thickness	0.254	.36
Average GC-IPL thickness	-0.066	.81
FAZ area, 3 mm x 3 mm	-0.150	.59
Perfusion density		
6-mm circle, 6 mm x 6 mm	0.208	.46
3-mm ring, 6 mm x 6 mm	0.089	.75
6-mm ring, 6 mm x 6 mm	0.222	.43
3-mm circle, 3 mm x 3 mm	0.255	.34
3-mm ring, 3 mm x 3 mm	0.252	.35
Vessel density		
6-mm circle, 6 mm x 6 mm	0.207	.46
3-mm ring, 6 mm x 6 mm	0.104	.71
6-mm ring, 6 mm x 6 mm	0.257	.35
3-mm circle, 3 mm x 3 mm	0.3	.26
3-mm ring, 3 mm x 3 mm	0.197	.46

** P value significant at < .05*

OCTA = optical coherence tomography angiography; MRI = magnetic resonance imaging; AD = Alzheimer's disease; MCI = mild congitive impairment; CST = central subfield thickness; GC-IPL = ganglion cell – inner plexiform layer complex; RNFL = retinal nerve fiber layer; FAZ = foveal avascular zone

were relatively similar with regard to years of education (16.4 years ± 1.9 years for the AD group and 15.0 years ± 2.4 years for the MCI group). All subjects underwent Mini-Mental State Exam (MMSE) cognitive testing. The mean MMSE score was 21.6 ± 3.0 for the AD group and 26.0 ± 1.4 for the MCI group (Table 1).

The OCT and OCTA parameters are provided in Table 2 and MRI volume parameters are provided in Table 3. There was a significant correlation between increased ILV volume and decreased VD in the 6-mm circle ($\rho = -0.565$, $P = .028$; n = 15) with an R^2 value of 0.48 (Beta –0.324, $P = .004$) and in the 3-mm ring ($\rho = -.569$, $P = .027$; n = 15) with an R^2 value of 0.48 (Beta –0.525, $P = .004$) on the 6 mm x 6 mm OCTA images. There was a significant correlation between PD in the 3-mm ring ($\rho = -0.6047$, $P = .0169$; n=15) on the 6 mm x 6 mm OCTA images. There was no significant association between ILV volumes and other VD or PD measures (all $P > .05$); however, all had a similar trend. The LV and HP volumes did not show a significant association between either VD or PD ($P > .05$) but LV had a similar trend as ILV. There was no significant association between ILV, LV, and HP volumes, forebrain parenchyma volume, cortical gray matter volume and FAZ area, CST, RNFL thickness, and GC-IPL thickness ($P > .05$). Spearman correlation coefficients and P values for all parameters are provided in Table 4. Figure 2 provides representative examples across the spectrum of severity of dementia and the corresponding brain volumes and retinal microvascular changes.

DISCUSSION

In this pilot investigation, we found that reduction of VD and PD in the 6 mm × 6 mm OCTA images was significantly associated with expansion of the ILV volume on brain MRI in AD and MCI. Although we had a small sample size, we are, to the best of our knowledge, the first to report an association of retinal microvascular OCTA parameters with volumetric brain MRI measures in AD and MCI subjects.

Hippocampal atrophy and passive expansion of the ventricles resulting from brain tissue loss are well recognized with AD and MCI in prior MRI studies.[5,16] Although ventriculomegaly is not a specific finding to AD, it has been observed at greater rates in AD subjects and has been correlated with a decline in cognitive function and cerebrospinal fluid (CSF) biomarkers as well as increased amyloid-beta burden.[14,16] Both HP volume and ILV volume derived from volumetric MRI have been utilized to estimate medial temporal atrophy and subsequent risk for conversion of MCI to AD.[17] Several prior studies have evaluated the correlation of OCT parameters, but not OCTA parameters, with brain MRI. Ong et al.[18] reported an association between GC-IPL thinning on OCT with decreased temporal lobe and occipital lobe volumes on MRI in 125 persons with cognitive impairment but no dementia, 36 who were cognitively normal, and three who had dementia. Also, den Haan et al. showed an association between total macular thickness and parietal cortical atrophy in a cohort of 15 early onset AD and 15 control subjects.[9] Casaletto et al. similarly reported an association between RNFL thinning, reduced total macular and GC-IPL volumes with smaller medial temporal lobe volumes on MRI in 79 neurologically normal adults.[19] Uchida et al. reported a significant correlation between ellipsoid zone to retinal pigment epithelium thickness on OCT and total brain volume on volumetric MRI in a cohort of 14 AD, 15 MCI, 12 non-AD dementia, 19 Parkinson's, and 31 control subjects.[20] In addition, Rotenstreich et al. found significant associations between macular RNFL and GC layer thicknesses with hippocampal volume on MRI and cognitive function in 77 asymptomatic offspring of AD patients compared to age-matched controls.[21] In our study, however, we did not find a significant association between volumetric brain MRI parameters and RNFL thickness, GC-IPL thickness, CST, or FAZ area, which may be due to our smaller sample size.

OCTA is a rapid and noninvasive imaging modality that may detect surrogate retinal biomarkers of alterations in the cerebral microcirculation related to AD pathology.[6,11] Bulut et al. found decreased SCP VD on OCTA in 26 AD subjects compared to 26 controls, whereas Jiang et al. showed reduced microvascular density of the superficial and deep capillary plexuses in 12 AD subjects compared to 21 controls through fractal analysis.[6,11] We recently confirmed a similar reduction in a larger cohort of 39 AD subjects, 37 MCI subjects, and 133 age matched controls.[22]

The reduction in retinal vessel density detected through OCTA may mirror changes occurring in the cerebral microcirculation of AD subjects and consequential hippocampal atrophy leading to ILV expansion. Reduced vessel caliber, decreased vessel density, and increased vessel tortuosity have been reported in brains of AD subjects and are thought to be associated with impaired amyloid-beta peptide clearance.[23,24] The use of cerebral ventricular volume as a measure of AD progression has been described.[16] Hemispheric atrophy rates, measured by ventricular enlargement, correlate more strongly with changes on cognitive tests than medial temporal lobe atrophy rates.[25]

Our study has several limitations. Because of the smaller sample size, it may be underpowered to detect associations between OCTA and volumetric brain MRI parameters. We were unable to compare the MCI

patients to the AD patients and there was no control group. Due to the cross-sectional design of the study, we could not assess if changes in OCTA parameters correlate with volumetric brain MRI changes over time. We did not have access to CSF biomarker data that might have helped to better quantify the associations.[26,27] Since this was exploratory pilot data, adjustment for multiple comparisons was not performed.

We observed a significant correlation between the ILV and the PD and VD in the 3-mm ring of the 6 mm x 6 mm OCTA scan, whereas the correlation between ILV and the PD and VD in the 3-mm ring of the 3 mm x 3 mm OCTA scan and ILV was not statistically significant. Although the 3-mm ring in the 6 mm x 6 mm scan technically measures the same area as the 3-mm ring in the 3 mm x 3 mm scan does (red areas in Figures 1B and 1D, respectively), there are some differences in the actual numerical values generated by these two scan protocols, as seen in Table 2. There are several possible reasons for this discrepancy. When the 3 mm x 3 mm OCTA scan pattern is used, there are 245 A-scans in each B-scan along the horizontal dimension and 245 B-scans along the vertical dimension. As a result, the interscan spacing between each A-scan and B-scan is 12.2 µm. When an OCTA image is acquired using the 3 mm x 3 mm scan pattern, each B-scan is repeated four times at the same position.[28] When using the 6 mm x 6 mm OCTA scan pattern, there are 350 A-scans in each B scan along the horizontal dimension and 350 B-scans along the vertical dimension. As a result, the interscan spacing between A-scan and B-scan is 17.1 µm. Each B-scan in the 6 mm x 6 mm scan is repeated twice at the same position.[28] It is therefore possible that the difference in the numerical values results in a difference in resolution between the two scan patterns. In addition, the inter-scan reproducibility of the OCTA measurements needs to be established in eyes with impaired retinal microvasculature such as in neurodegenerative diseases and may also be a potential confounding factor. Finally, a larger sample size is essential to validate these findings.

In conclusion, there was a significant association between decreased VD and PD on OCTA images of the SCP and increased ILV volume on volumetric brain MRI in subjects with AD and MCI. These data suggest that retinal microvascular changes in AD and MCI detected by OCTA may mirror volumetric changes in the brain and may potentially serve as an additional screening, diagnosis, and monitoring tool. Investigation with a larger cohort is needed to validate these findings and further elucidate the association of retinal microvasculature changes with volumetric brain MRI changes in AD and MCI.

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