Deep Segmentation of OCTA for Evaluation and Association of Changes of Retinal Microvasculature with Alzheimer's Disease and Mild Cognitive Impairment

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Synopsis/Precis: we propose a standardized framework for automated analysis of OCTA images and demonstrate its suitability by investigating the microvascular and FAZ alterations in and between Alzheimer's Disease and Mild Cognitive Impairment and healthy controls.

Abstract

Background: Optical coherence tomography angiography (OCTA) enables fast and non-invasive high-resolution imaging of retinal microvasculature and is suggested as a potential tool in the early detection of retinal microvascular changes in Alzheimer's Disease (AD). We developed a standardized OCTA analysis framework and compared their extracted parameters among controls and AD/ Mild Cognitive Impairment (MCI) in a cross-section study.

Methods: We defined and extracted geometrical parameters of retinal microvasculature at different retinal layers and in the foveal avascular zone (FAZ) from segmented OCTA images obtained using well-validated state-of-the-art deep learning models. We studied these parameters in 158 subjects (62 healthy control, 55 AD, and 41 MCI) using logistic regression to determine their potential in predicting the status of our subjects.

Results: In the AD group, there was a significant decrease in vessel area and length densities in the inner vascular complexes (IVC) compared to controls. The number of vascular bifurcations in AD is also significantly lower than that of healthy people. The MCI group demonstrated a decrease in vascular area, length densities, vascular fractal dimension, and the number of bifurcations in both the superficial vascular complexes (SVC) and the IVC compared to controls. A larger vascular tortuosity in the IVC, and a larger roundness of FAZ in the SVC, can also be observed in MCI compared to controls.

Conclusion: Our study demonstrates the applicability of OCTA for the diagnosis of AD and MCI, and provides a standard tool for future clinical service and research. Biomarkers from retinal OCTA images can provide useful information for clinical decision-making and diagnosis of AD and MCI.

What is already known on this topic - Retinal microvascular changes in optical coherence tomography angiography (OCTA)

are believed as potential biomarkers for AD and MCI diagnosis, but the variations in equipment being used, statuses of patients, and analysis methodology caused inconsistent results among published papers.

What this study adds - Developed a new automated standardized framework, driven by the recent advancements in deep learning, which can automatethe extraction of 12 retinal parameters from OCTA images, and further investigated their potential as retinal biomarkers for Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI).

How this study might affect research, practice or policy – We provides a standard tool for OCTA analysis, which can be used in future clinical service and research in AD and other applications.

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1. Background

The retina and the brain share similar physiological characteristics, embryology origin, precise neuron cell layers and microvasculature. With the increasing prevalence of Alzheimer's disease (AD) worldwide, recent reports suggest the retina as a potential route to evaluate and monitor the disease progression. Accumulating retinal imaging reports using different imaging tools suggested the neuronal integrity and microvasculature of the retina reflect that of the brain.[1, 2] Compared with the current diagnostic gold standards such as positron emission tomography (PET) and spinal-fluid examination, retinal imaging is faster, non-invasive, affordable and accommodating to patients.[3] Reports suggested that the retina can be used as a window to study (AD) and other common neurodegenerative diseases.[4–6]

With the vast improvement in resolution of images and the accessibility of ophthalmologic imaging tools, application of new, high resolution imaging tools such as the optical coherence tomography angiography (OCTA) have enabled the in vivo visualization of the retinal microvasculature.[Error! Bookmark not defined.,7] Of note, the use of OCTA in the early detection of retinal microvascular changes in AD is an area receiving growing scientific attention as witnessed by the sheer increase in the number of reports in the past few years.[8-16] However, there are inconsistencies across these reports, which may due to the variations of equipment used, statuses of patients and most importantly methodology of analysis. The development of computational tools, such as deep learning algorithms has enhanced the potential of data-rich retinal imaging as a promising tool and a potential biomarker for AD.

In this study, we proposed a new standardized framework, driven by advances in deep learning for automated analysis of OCTA images. We extracted 12 different parameters characterizing both retinal microvasculature and FAZ. We also assessed the correlation between retinal microvascular changes and clinical features in AD and MCI.

2. Method

The clinical protocol of our study was approved by the ethics committee of the Cixi Institute of Biomedical Engineering, Chinese Academy of Sciences, and adhered to the principles of the Declaration of Helsinki. The study was conducted at the Affiliated People's Hospital of Ningbo University Hospital and Peking University Third Hospital. Participants enrolled in our study provided informed written consent.

2.1 AD and MCI Participants

Enrolled patients meet the National Institute of Aging and Alzheimer's criteria[17] for probable AD and the Petersen criteria[18] for MCI. Experienced neurologist made the diagnosis for the AD/MCI subjects, specifically, enrolled AD patients had MMSE scores within 13 – 20 while MCI patients had MMSE scores within 21 – 24. The criteria for exclusion of participants were those with neurodegenerative diseases (such as Parkinson's disease), psychiatric disease, toxic or metabolic disease, infectious disease, ophthalmic disease (examined by an experienced ophthalmic according to the fundus and OCTA images of the patients without knowing their health statuses) which could not permit the imaging of the macula (severe glaucoma and cataract), diabetic retinopathy, corneal opacities, elevated intraocular pressure, optic neuropathy or high myopia (>6.0 D).

2.2 Control group

Healthy participants had similar educational background, age and sex to the AD and MCI participants. Participants were excluded if they were hypotensive, or uncontrolled hypertensive; experienced neurological disorders; or reported current or previous substance abuse. All received MMSE examination and had scores of over 24

2.3 OCT Angiography Image Acquisition

Macula microvascular imaging was acquired with using OCTA device (Avanti RTVue XR, Optovue, Inc., Fremont, CA, USA, software version 2017.1.0.151). The imaging camera is capable of scanning at 70,000 A-scans/s with an axial resolution of 5 μm and a light source with wavelength 840 ± 10 μm. The macula of each participant was assessed by using B-scans covering an area of 3 × 3 mm^2 and 6 × 6 mm^2 horizontally and vertically. An inbuilt software in the OCTA camera was used to project the macula microvasculature into the superficial vascular complex (SVC), deep vascular complex (DVC) and inner retinal vascular complex (IVC), as shown in **Figure 1(b)**. The OCTA tool (software version 2017.1.0.151) was incorporated with a three-dimensional Projection Artifact Removal (3D PAR) to reduce projection artifacts in the deeper capillary plexus while preserving the authentic layout. The SVC and DVC were set in the inner two-thirds and the outer one-third interface of the ganglion cell layer and inner plexiform layer. IVC consists of the SVC and DVC and was defined as 5μm above the inner limiting membrane (ILM) to 25 μm below the border of the inner nuclear layer (INL), as shown in **Figure 1(a)**.

2.4 Deep learning-based Extraction of Microvasculature and FAZ

We proposed a standard tool for the automated analysis of OCTA images: Two deep learning-based approaches are employed for the accurate segmentation of microvasculature and FAZ from OCTA images, respectively. The segmentations will be used to extract the parameters of interest of microvasculature and FAZ thereafter.

Microvasculature segmentation

We utilized a state-of-the-art method, OCTA-Net[19] for microvasculature segmentation in OCTA images. This model consists of a split-based coarse segmentation and a split-based refining segmentation module, with the goal of producing a preliminary confidence map, and optimizing the contour of the retinal microvasculature, respectively. The OCTA-Net was trained on a public OCTA dataset named ROSE-1, and its efficiency has been validated, with its AUC>0.94.[19] The dataset contains 117 OCTA *en face* angiograms (example shown in **Figure 1(c)**) acquired using the RTVue XR Avanti SD-OCT system. Clinicians manually annotated all microvasculatures as the ground truth at pixel and centerline level. In this study, 60 images were used for training the OCTA-Net and the rest for testing. **Figure 1(d)** illustrates an example of the microvascular segmentation. We have provided more details about the OCTA-Net in **Appendix-I**.

FAZ segmentation

A gate-based feature integration deep network (FAZ-Net) is employed for the FAZ segmentation[20]. This method was inspired by an ensemble model.[21] Three encoders are designed to obtain features intelligently integrated by voting to enhance the robustness and representation ability of features. We invited a senior ophthalmologist to manually trace the FAZ boundary in each OCTA image of the ROSE-1 dataset. We used 60 images for training and the rest for testing the FAZ-Net. The segmentation performance has shown its robustness and effectiveness, with Dice>0.95. **Figure 1(k)** illustrates an example of the FAZ segmentation. The brief descriptions of the FAZ-Net are provided in **Appendix-II**.

2.5 Definitions of quantitative parameters

We defined and investigated 12 parameters that represent the distribution, topology, orientation and shape of both microvasculature and the FAZ, as illustrated in **Figure 1**.

Vascular-related parameters

·**Vascular Area Density (VAD)**: the total length in millimeters of perfused retinal microvasculature per unit area in square millimeters in the annular region of the analyzed area;[16]

·**Vascular Length Density (VLD)**: the ratio between the total number of pixels of microvascular centerlines (shown in **Figure 1(e))** and the area of the analyzed region;

·**Vascular Fractal Dimension (VFD)**: a well-known measure of the geometric complexity of vasculature, as shown in **Figure 1(g)**;

·**Vascular Tortuosity (VT)**: a metric to measure the tortuous level of the vasculature as shown in **Figure 1(i)**, computed by applying the method proposed by Zhao et al.; [22]

·**Vascular Bifurcation Number (VBN)**: the total number of bifurcations, which are determined by locating the intersection points of the vessel map at centerline-level, as shown in **Figure 1(f)** (pixels with more than two neighbors);

·**Vascular Orientation Distribution (VOD)**: calculates the direction of each vascular pixel to indicate the trend of the blood flow, as shown in **Figure 1(h)**. More details about VOD are in Appendix-III;

·**Arterioles and Venules caliber Ratio (AVR)**: the ratio of mean calibers between arterioles and venules. Note that the AVR is calculated in $6\times6mm^2$ OCTA images only, by using the method proposed by Xie et al.[23] to distinguish automatically between arteries and veins, as shown in **Figure 1(j)**.

FAZ-related parameters

·**FAZ Area (FA)**: the total number of pixels in the FAZ region;

·**FAZ Axis Ratio (FAR)**: the ratio between the major and minor axes of the fitted ellipse from the FAZ boundary, as shown in **Figure 1(m)**. A higher FAR indicates an elongated FAZ with greater eccentricities;

·**FAZ Circularity (FC)**: the degree of roundness of the FAZ.[24] The larger the FC value, the more circular the shape. A value of 1.0 denotes a perfect circle;

·**FAZ Roundness (FR)**: similar to FC, but is less sensitive to irregular borders along the perimeter (shown in **Figure 1(l)**) of FAZ;

·**FAZ Solidity (FS)**: describes the extent to which the FAZ is convex or concave as shown in **Figure 1(n)**, and is defined as the ratio between the FA and the convex area covering the FAZ. The further the solidity deviates from 1, the greater the extent of concavity in the structure.

2.6 Statistical analyses

In this study, only one eye per individual was used for the analysis, to avoid between-eye correlation. The eye with higher signal strength intensity (SSI) and visual acuity (VA) was selected when images of both eyes are available. The demographic variables of enrolled participants and the extracted OCTA parameters were compared across the three groups. If the samples across each group met the hypothesis of homogeneity of variance, one-way analysis of variance (ANOVA) was performed for continuous variables; otherwise, a non-parametric test was applied for continuous variables and a Chi-square test for categorical variables. Furthermore, considering the impact of confounding factors (such as image quality, other eye disease et. al), OCTA parameters

were modelled using the continuous and multivariate logistic regression (MLR) method. The Bonferroni correction was performed in our result. In practice, the P Value for SVC and IVC was corrected by 24, and the P value for DVC was corrected by 12. All statistical analyses were performed using the SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA), and $P < 0.05$ (2-sided) was considered statistically significant.

3. Results

3.1 Descriptive Statistics

A total of 55 AD, 62 healthy control (HC) and 41 MCI participants were enrolled. 10 AD and 3 HC participants were excluded, because of low signal quality during imaging and/or presence of imaging artifacts. This analysis thus consisted of 45 eyes of AD participants, 41 eyes of MCI and 59 eyes of HC.

As shown in **Table 1**, there are no significant difference ($P \geq 0.05$) in terms of age and diabetic status among the three groups in the ANOVA analysis. In the univariate logistic regression analysis, the MCI patients are older than the controls, but there is no significant age difference between AD and healthy controls. There is a significant difference in gender ratios ($P = 0.029$) between the three groups. The univariate logistic regression analyses showed that both the AD and MCI groups have significantly reduced MMSE scores ($P < 0.001$) compared with HC. Due to the incomplete demographic information of the MCI group, the education level, hypertension and SSI parameters were only compared between AD and HC groups. A significant difference ($P < 0.05$) is found in education level, while there is no significant difference in hypertension and SSI ($P > 0.05$) between the AD and HC groups.

The OCTA parameters were compared within the three groups: the results are shown in **Table 2**. In the DVC, VAD, VLD and VFD are significantly reduced ($P < 0.05$) in AD and MCI when compared to HC, and the FR shows a significant difference ($P = 0.014$) between the three groups. In the SVC, there are significant differences in VAD, VLD, VFD, VB and FR ($P < 0.05$) among the three groups. In the IVC, there are no significant difference in FAZ- related parameters between AD, MCI and controls, while the VAD, VLD, VFD, and VB showed significant decreases ($P < 0.05$) in AD and MCI compared to HC participants. Of note, VT in IVC shows significant difference among the three groups ($P = 0.007$).

In the 6×6 mm^2 fovea-centered scans, no significant differences among the three groups are found in AVR.

3.2 Logistic Regression Analysis

After adjusting the demographic data, the results of the MLR analysis are shown in **Table 3**. In the DVC, the changes in OCTA parameters are not significantly associated ($P \geq 0.05$) with the presence of MCI or AD. In the SVC, the decrease of VAD, VLD, VFD and VB, and the change in FR shows a significant correlation ($P < 0.05$) with the presence of MCI. In the IVC, decreased

VAD, VLD and VB significantly correlate with the presence of AD or MCI ($P < 0.05$). Furthermore, increased VT and decreased VFD only show significant correlation ($P < 0.05$) with the presence of MCI. There was no association between changes in FAZ-related-parameters and AD or MCI ($P \geq 0.05$).

4. Discussion

4.1 Microvascular alterations in AD individuals versus in healthy controls

In our present study, OCTA techniques are used to analyze the retinal vascular morphology and vascular density in AD, MCI and controls. The AD participants show decreased microvascular density and damage vascular morphology in terms of VAD, VLD and VB in the IVC when compared to controls, whereas there is no significant structural difference in the DVC and SVC. Although our findings are not in line with most OCTA studies shown in Table 4, our study suggests that microvascular impairment occurs in the pathogenesis of AD.

Our results in **Table 3** show that AD participants have a s impaired microvascular morphology and densities in the SVC and DVC, but no significant difference is observed. This finding is discordant with the conclusions of most previous studies,[9–11, 13, 15, 16] where AD participants showed a decrease in microvascular density compared with controls. However, there are also some studies that support our result.[12, 14] Possible explanations for this phenomenon are suggested below.

On one hand, the decreasing density of the vasculature may be due to β- Amyloid (A-β) deposits, which have been reported by Brown et al.[25] In their work, they argued that A-β deposition around vascular walls disrupts the basement mem- brane of small vessels, causing endothelial damage and thus reducing angiogenesis. Firstly, the decreasing density of vasculature observed in our study did not reach a significant level. This may be related to several confounders. First, the absence of motion artefacts and high software-derived image quality scores (>6/10) were necessary to obtain good or excellent repeatability for performing the vascular measurement.[26] In our study, images with scan qualities below 7, or with artefacts were excluded, and the SSIs are thus highly similar between the AD group and the controls (8.26 VS 8.07). Secondly, differences in the instruments and embedded software used may cause inconsistencies between different studies. Spaide et al.[27] analyzed three different instruments (Carl Zeiss, Optovue and Topcon) in terms of the segmentation slab, designed to isolate the superficial vascular plexus and the deep vascular plexus, and pointed out that three different instruments produced differing segmentation results. Meanwhile, when directly comparing the images captured by OCTA with the vascular patterns in an autopsied eye, they concluded that none of the instruments produced segmented regions that correctly followed the relevant anatomic layers.

The IVC in our study was the layered combination of DVC and SVC, and the vascular parameters of AD participants showed significant decrease when compared with controls. This may be attributed to the accumulation of the different changes in the

SVC and DVC, as the changes in value in the SVC and DVC when considered separately did reach a significant level in our study. Therefore, vasculature parameter measurement in the IVC may be more promising in investigating the AD. However, there is only one study[13] working on the IVC slab, and in this work the SSI was not adjusted.

4.2 Microvascular alterations in MCI individuals versus in healthy controls

Our results imply that MCI participants exhibit significant vessel loss (i.e., decreases in VAD, VLD, VFD and VB values) in the SVC when compared with control participants, but no significant vasculature decrease is observed in the DVC, which supports some of the previous findings in MCI participants.[15, 16] This finding may indicate that the SVC, which is responsible for the metabolic demands of the parafoveal ganglion cell layer (GCL),[28, 29] is the target of pathology in MCI. Therefore, we conjecture that the change in the DVC may occur after the alteration in the SVC. However, there are studies[13, 14] that reach the opposite conclusion: capillary alterations occur only in the DVC.

Conflicting results within different studies may be due to other reasons. Except for the effects of varied image quality, artefacts and instruments, the inconsistent results between previous studies may be also due to excessively vague selection standards for the MCI participants. MCI is a period during which, as cognitive decline gradually progresses from normal to dementia, individuals may suffer from a wide range of cognitive impairments, even if they can still carry out their activities of daily living with no help from others.[30] Therefore, the heterogeneity of vascular alterations in different stages of MCI may explain inconsistent findings between studies. In addition, MCI vasculature alteration in the IVC may be more predictive than in the other two slabs, as we observed significant decreases in VAD, VLD, VFD, VB and VT values in the IVC.

4.3 FAZ alterations between AD/MCI and control

In our study, there is no association between AD/ MCI and FAZ-related parameters in all three plexuses except for the FR in the SVC of MCI. Our finding contradicts the findings of some previous studies (Table 4). This inconsistency may be multifaceted since the FAZ area has numerous limitations when considered a potential biomarker. For example, some studies[31] have shown that age, gender and eyeball axial length can affect the FAZ area. Therefore, it is necessary to adjust the age, gender and axial length parameters when analyzing FAZ-related parameters between different groups. To this end, age and gender were adjusted in this study for the multivariate regression analysis, which may explain why our findings differ from those of others. In addition, the significant alteration of FR in the SVC may support the conclusion that the roundness of the FAZ may be a potential biomarker in MCI diagnosis, as this parameter is less related to the absolute size of the FAZ, and to the axial length of the eyeball.

4.4 Limitations

This study has several limitations. First, despite employing the largest participant cohort of any related study, the number of participants is still relatively small. A cross-sectional study does not measure changes in retinal microvascular parameters over time or disease progression. Longitudinal studies in larger cohorts must determine whether these findings are a reliable method for identifying AD/MCI patients in the pre-clinical stage. Secondly, the data on eyeball axial length, usually used to identify myopia, was not acquired in this study: this may influence the area of OCTA captured, and thus introduce bias in estimating the vascular parameters, and subsequent analysis. However, all patients with high myopia were excluded from the study, we expect that the effects of axial length might be limited. Finally, some risk factors for MCI are lost and are not adjusted in MLR analysis, which might be optimized in future work.

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Jianyang Xie contributed to the experimental design, OCTA analysis, clinical analysis, and manuscript writing. Yufei Wu, Yanwu Xu, Quanyong Yi and Qinkang Lu contributed to the revision and provided important intellectual content. Yufei Wu and Hong Qi contribute to the ophthalmic examination for participation and experimental design. Yalin Zheng, Yonghuai Liu, Antonella Macerollo, Ardhendu Behera and Alejandro F. Frangi contribute to the manuscript writing. Huazhu Fu and Jiang Liu contributed to the experimental design and manuscript writing. Jiong Zhang contribute to the OCTA analysis. Chenlei Fan contributes to the diagnosis of AD/MCI subjects. Yitian Zhao contributes to the experimental design, OCTA analysis and manuscript writing.

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Figure 1 Vascular- and foveal avascular zone (FAZ)-related parameters used in the quantitative measurements. (a) illustrates a B-scan of a sample OCT volume with retinal layers illustrated. (b) are en face angiograms of superficial vascular complexes (SVC), deep vascular complexes (DVC) and inner vascular complexes (IVC), respectively. (c) shows a 3×3 mm^2 *en face* SVC angiogram. (d) and (e) show the automated segmented vessel map and vessel skeleton map of (c), respectively. By calculating the ratio of vasculatures in (d) and (e), vascular area density (VAD) and vascular length density (VLD) can be derived, respectively. The red dots in (f) indicate the vascular bifurcations (VB). (g)-(j) illustrate vascular fractal dimension (VFD), vascular orientation distribution (VOD), vascular tortuosity (VT), and arterioles/venules (AV) classification, respectively. (Note: the AV classification is only applied to the 6×6 mm^2 *en face* angiogram in this work.) (k) is the detected FAZ area (FA), and (l) shows its perimeter (FP). The Circularity of the FAZ (FC) is calculated as: $FC = 4\pi * FA/FP^2$. (m) shows the major and minor axes of the fitted ellipse of the FAZ. The axis ratio of the FAZ (FAR) is defined as the ratio between major axial length L_{major} and minor axial length L_{minor}, while the roundness of the FAZ (FR) is calculated via $FR = 4\pi * FA/L^2$. (n) shows the convex area of the FAZ, and the solidity of the FAZ (FS) is defined as the ratio between the FA and the convex area.

Table 1 Results of univariate logistic regression for demographic data

Variable	HC(N=59) Mean(SD)	MCI(N=41)				AD(N=45)				P
		Mean(SD)	OR	95%CI	P_1	Mean(SD)	OR	95%CI	P_2	
Age, year	58.73(6.91)	61.73(7.84)	1.064	1.004-1.128	**0.038**	60.60(6.265)	1.040	0.983-1.100	0.175	0.098†
Number of Females (%)	35(46.7)	14(34.1)	0.356	0.155-0.814	**0.014**	26(57.8)	0.938	0.427-2.062	0.874	**0.029**$^{\perp}$
MMSE	26.52(3.14)	21.09(3.91)	0.685	0.586-0.799	**<0.001**	13.89(5.40)	0.497	0.401-0.617	**<0.001**	**<0.001**‡
Diabetes (%)	2(3.3)	2(4.9)	0.684	0.092-5.065	0.710	2(4.4)	0.737	0.100-5.445	0.765	0.928$^{\perp}$
Education level	1.441(0.82)	–	–	–	–	1.977(1.09)	1.831	1.179-2.844	**0.007**	**0.004**‡
Hypertension	13(21.3)	–	–	–	–	3(7.3)	4.252	1.139-15.865	**0.031**	0.057*
SSI	8.26(0.83)	–	–	–	–	8.07(0.85)	0.568	0.357-0.902	**0.017**	0.368*

[1] NOTE. MMSE: Mini Mental State Examination; SSI: signal strength intensity; HC: healthy controls; AD: Alzheimer's Diseases; MCI: Mild Cognitive Impairment. Continuous variables were described by mean (standard deviation), and frequencies (percentages) were used to describe categorical variables.

[2] NOTE. P_1 and P_2 were calculated by univariate logistic regression analysis between MCI and HC, AD and HC respectively. P was a comparison result among the three groups of AD, MCI and HC, where the $P^{\dagger}$ value was obtained by ANOVA; the $P^{\perp}$ value was obtained via chi-square test; the $P^{\ddagger}$ value was obtained nonparametric tests and the P^{*} value was obtained by Student's t-test.

Table 2 Comparisons of OCTA parameters between healthy control, MCI and AD participants

Variable	DVC				SVC				IVC			
	AD	MCI	Control	P	AD	MCI	Control	P	AD	MCI	Control	P
VAD	23.82(4.98)	22.06(4.67)	25.06(5.05)	**0.027**	15.51(2.25)	15.35(2.59)	16.65(2.32)	**0.014**	15.72(3.24)	16.03(3.36)	18.06(2.92)	**<0.001**
VLD	9.32(1.83)	8.70(1.71)	9.81(1.80)	**0.027**	5.74(0.89)	5.61(1.00)	6.17(0.92)	**0.009**	5.92(1.30)	5.98(1.31)	6.85(1.14)	**<0.001**
VFD	1.58(0.05)	1.57(0.06)	1.59(0.04)	**0.022**	1.49(0.04)	1.48(0.04)	1.50(0.03)	**0.017**	1.49(0.05)	1.49(0.05)	1.52(0.04)	**0.001‡**
VT	1.56(0.12)	1.54(0.15)	1.54(0.13)	0.577	1.80(0.22)	1.86(0.30)	1.73(0.26)	0.059	1.86(0.33)	1.87(0.27)	1.70(0.28)	**0.007**
VB	243(68)	220(64)	249(64)	0.433	141(36)	133(38)	157(35)	**0.003**	134(41)	132(36)	161(36)	**<0.001**
VOD	0.80(0.03)	0.80(0.04)	0.79(0.04)	0.486	0.85(0.06)	0.85(0.05)	0.85(0.06)	0.942	0.84(0.06)	0.84(0.06)	0.83(0.07)	0.952
AVR	—	—	—	—	—	—	—	—	0.99(0.06)	0.10(0.07)	0.99(0.08)	0.761
FA	0.37(0.12)	0.33(0.11)	0.34(0.12)	0.354	0.75(0.21)	0.65(0.26)	0.69(0.20)	0.129	0.39(0.14)	0.35(0.12)	0.37(0.12)	0.462
FAR	1.07(0.28)	1.20(0.18)	1.12(0.19)	0.144	1.13(0.39)	1.17(0.55)	1.22(0.22)	0.431	1.20(0.39)	1.15(0.25)	1.14(0.25)	0.555
FR	40.03(9.29)	34.79(4.82)	37.57(7.03)	**0.014‡**	39.58(10.75)	40.30(13.27)	34.42(7.00)	**0.010‡**	36.26(8.41)	37.26(8.73)	37.27(7.50)	0.501
FC	0.95(0.12)	0.99(0.11)	0.98(0.11)	0.205	0.70(0.11)	0.71(0.17)	0.74(0.111)	0.081‡	0.93(0.12)	0.94(0.14)	0.93(0.13)	0.936
FS	0.93(0.04)	0.94(0.04)	0.94(0.03)	0.602	0.85(0.03)	0.86(0.06)	0.86(0.05)	0:357‡	0.92(0.04)	0.92(0.06)	0.92(0.05)	0.100

[1] Note: the P value was obtained by ANOVA; the P‡ value was obtained by nonparametric tests. AVR was analyzed in the 6×6mm^2 fovea centered scans.

[2] NOTE. SVC: superficial vascular complexes, DVC: deep vascular complexes, IVC: inner vascular complexes. VAD: vascular area density, VLD: vascular length density, VB: vascular bifurcations (VB), VFD: vascular fractal dimension, VOD: vascular orientation distribution, VT: vascular tortuosity (VT), AVR: arterioles/venules diameter ratio. FA: FAZ area, FP: FAZ perimeter (FP), FC: Circularity of the FAZ, FAR: axis ratio of the FAZ, FR: roundness of the FAZ, FS: solidity of the FAZ.

Table 3 Results of multivariate logistic regression analysis

Variable		DVC			SVC			IVC		
		OR	95%Cl	P	OR	95%Cl	P	OR	95%Cl	P
VAD	MCI	0.906	0.817 to 1.004	0.059	0.812	0.667 to 0.989	**0.038**	0.823	0.707 to 0.959	**0.013**
	AD	0.957	0.800 to 1.146	0.635	0.825	0.629 to 1.082	0.164	0.699	0.661 to 0.965	**0.020**
VLD	MCI	0.752	0.565 to 1.002	0.052	0.564	0.341 to 0.934	**0.026**	0.586	0.396 to 0.868	**0.008**
	AD	0.934	0.525 to 1.663	0.816	0.680	0.337 to 1.372	0.282	0.575	0.354 to 0.934	**0.025**
VFD	MCI	0.000	0.000 to 5.314	0.097	0.006	0.000 to 0.384	**0.036**	0.003	0.000 to 0.069	**0.014**
	AD	0.030	0.003 to 1.173e^{5}	0.651	0.001	0.000 to 4.212e^{4}	0.421	0.010	0.000 to 1.929	0.063
VT	MCI	0.477	0.020 to 11.407	0.648	8.393	0.917 to 31.709	0.062	7.542	1.251 to 45.461	**0.027**
	AD	3.065	0.609 to 15.424	0.174	2.291	0.231 to 22.751	0.479	3.449	0.532 to 22.382	0.194
VB	MCI	0.995	0.988 to 1.003	0.201	0.981	0.968 to 0.995	**0.007**	0.980	0.967 to 0.993	**0.002**
	AD	0.993	0.975 to 1.011	0.430	0.987	0.969 to 1.005	0.162	0.984	0.970 to 0.998	**0.023**
VOD	MCI	1.382e^{3}	0.006 to 3.370e^{8}	0.253	11.056	0.005 to 2.284e^{4}	0.537	2.641	0.002 to 2.940e^{3}	0.786
	AD	0.046	0.000 to 4.995	0.198	0.609	0.000 to1.295e^{3}	0.899	6.747	0.004 to 1.151e^{4}	0.615
AVR	MCI	—	—	—	—	—	—	7.409	0.009 to 5.851e^{3}	0.468
	AD	—	—	—	—	—	—	1.226	0.003 to 0.511e^{3}	0.947
FA	MCI	0.739	0.275 to 1.986	0.548	0.790	0.470 to 1.329	0.374	0.712	0.281 to 1.80^{3}	0.474
	AD	10.500	0.000 to 5.566e^{5}	0.672	1.499	0.839 to 2.679	0.172	1.811	0.726 to 4.518	0.203
FAR	MCI	3.257	0.428 to 24.789	0.254	0.392	0.227 to 2.111	0.518	1.224	0.245 to 6.102	0.805
	AD	1.042	0.835 to 1.300	0.716	0.443	0.108 to 1.825	0.260	1.265	0.280 to 5.713	0.760
FR	MCI	0.942	0.875 to 1.013	0.107	1.069	1.107 to 1.123	**0.008**	0.992	0.941 to 1.046	0.771
	AD	1.000	0.999 to 1.001	0.714	1.052	0.994 to 1.113	0.081	0.998	0.942 to 1.058	0.952
FC	MCI	2.744	0.061 to 122.695	0.603	0.147	0.005 to 4.360	0.268	3.306	0.107 to 102.420	0.495

	AD	0.424	0.049 to 3.696	0.437	0.084	0.001 to 6.011	0.255	4.193	0.104 to 169.616	0.448
FS	**MCI**	0.191	0.004 to 2.095e[4]	0.315	0.022	0.006 to 190.172	0.408	0.347	0.041 to 1.980e[3]	0.811
	AD	22.168	0.126 to 3.911e[3]	0.240	0.007	0.001 to 446.681	0.380	50.296	0.001 to 1.722e[6]	0.462

[1] Note: P value of AD was adjusted for age, education level, hypertension and signal strength of OCTA scans; P value of MCI was adjusted for age, gender and diabetes. AVR was analyzed only for the 6×6mm^2 OCTA images.
[2] NOTE. SVC: superficial vascular complexes, DVC: deep vascular complexes, IVC: inner vascular complexes. VAD: vascular area density, VLD: vascular length density, VB: vascular bifurcations (VB), VFD: vascular fractal dimension, VOD: vascular orientation distribution, VT: vascular tortuosity (VT), AVR: arterioles/venules diameter ratio. FA: FAZ area, FP: FAZ perimeter (FP), FC: Circularity of the FAZ, FAR: axis ratio of the FAZ, FR: roundness of the FAZ, FS: solidity of the FAZ.

Table 4 Optical coherence tomography angiography studies on individuals with Alzheimer's disease and mild cognitive impairment

Authors	Participants	OCTA device	Scan area mm^2	Parameters	SVC	DVC	IVC
Elizabeth et al.[8]	14 AD 16 control	RTVue XR Avanti	8×8	FA	Not analyzed.	Not analyzed.	FAZ ↑ in AD
Bulut et al.[9]	26 AD 26 control	RTVue XR 100-2	6×6	VAD, FA	VAD ↓ in AD FA ↑ in AD	Not analyzed.	Not analyzed.
Yoon et al.[10]	39 AD 37 MCI 133 control	Cirrus HD-5000	3×3 6×6	VAD, FA	VAD ↓ in AD	Not analyzed.	Not analyzed.
Lahme et al.[11]	36 AD 38 control	RTVue XR Avanti	3×3	VAD	VAD ↓ in AD	No significant difference.	Not analyzed.
Zabel et al.[12]	27 AD 27 control	RTVue XR Avanti	6×6	VAD, FA	No significant difference.	VAD ↓ in AD FA ↑ in AD	Not analyzed.
Jiang et al.[13]	12 AD 19 MCI 21 control	Cirrus HD-5000	3×3 6×6	VFD	VFD ↓ in AD	VFD ↓ in AD VFD ↓ in MCI	VFD ↓ in AD
Wu et al.[14]	18 AD 21 MCI 21 control	RTVue XR Avanti	6×6	VAD, FA	No significant difference.	VAD ↓ in AD VAD ↓ in MCI FA ↑ in AD FA ↑ in MCI	Not analyzed.
Zhang et al.[15]	16 AD/MCI 16 control	RTVue XR Avanti	3×3	VAD, VLD	VAD ↓ in AD VAD ↓ in MCI	No significant difference.	Not analyzed.
Chua et al.[16]	24 AD 37 MCI 29 control	Cirrus HD-5000	3×3	VAD, VFD FA	VAD ↓ in AD VAD ↓ in MCI	VAD ↓ in AD	Not analyzed.
Our work	45 AD 41 MCI 59 control	RTVue XR Avanti	3×3 6×6	As shown in section 2.5.	VAD ↓ in MCI VLD ↓ in MCI VFD ↓ in MCI VB ↓ in MCI FR ↑ in MCI	No significant difference.	VAD ↓ in MCI, AD VLD ↓ in MCI, AD VB ↓ in MCI, AD VFD ↓ in MCI VT ↑ in MCI

[1] Note: ↑ and ↓ represent a significant increase and decrease compared to the control group. The parameters used have been detailed in section 2.5.
[2] NOTE. SVC: superficial vascular complexes, DVC: deep vascular complexes, IVC: inner vascular complexes. VAD: vascular area density, VLD: vascular length density, VB: vascular bifurcations (VB), VFD: vascular fractal dimension, VOD: vascular orientation distribution, VT: vascular tortuosity (VT), AVR: arterioles/venules diameter ratio. FA:

FAZ area, FP: FAZ perimeter (FP), FC: Circularity of the FAZ, FAR: axis ratio of the FAZ, FR: roundness of the FAZ, FS: solidity of the FAZ.