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Retinal Vessel Density Correlates with Cognitive Function in Older Adults

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Abstract

Purpose: We examined the associations between retinal microvascular density, cognition, and physical fitness in healthy older adults with no reported cognitive decline.

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Credit Author Statement

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Methods: Twenty cognitively normal older adults (age: 70.3 ± 4.6 years) were recruited. Both eyes of each subject were imaged using optical coherence tomography angiography. The vessel densities of the retinal vascular network (RVN), superficial vascular plexus (SVP), and deep vascular plexus (DVP) were measured. Cognitive function was assessed using the Mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA), while physical performance was evaluated using the total work during the YMCA cycle ergometer test (TW-YMCA). Spearman correlations (r_s) were computed between measures of retinal microvascular density, cognitive function, and physical performance.

Results: The MoCA was significantly correlated to vessel density of SVD ($r_s = 0.53$, $P = 0.02$) but not RVN ($r_s = 0.39$, $P = 0.09$) and DVP ($r_s = 0.02$, $P = 0.93$). MoCA was not correlated with TW-YMCA ($r_s = 0.05$, $P = 0.83$). Retinal microvascular densities were not related to TW-YMCA ($r_s = -0.05 \sim 0.18$, $P > 0.05$). Additionally, MMSE was not related the retinal vessel densities ($r_s = -0.10 \sim 0.21$, $P > 0.05$) and TW-YMCA ($r_s = -0.19$, $P = 0.41$).

Conclusions: This is the first study to reveal the association between retinal vessel density and cognition as measured with MoCA in healthy older adults with no reported cognitive decline.

Keywords

retinal microvasculature; cognition; older adults; fitness

INTRODUCTION

There are more than 50 million people with dementia worldwide, and there are approximately 10 million new cases every year.[1] Dementia predominantly affects older adults and is one of the major causes of disability, leading to a substantial burden on society and high healthcare costs.[1] Accumulating evidence indicates that microvascular alterations in the brain, especially at the capillary level,[2–4] are one of the major pathogenic contributors to cognitive impairment and dementia in older adults.[5,6] These cerebral small vessel alterations have been reported to correlate with cognitive decline.[7] The ability to detect cerebral vascular alterations at a micro-vessel level in patients with varying degrees of cognitive impairment would allow monitoring of the disease progression and intervention efficacy.[8] However, it is difficult and decidedly expensive to visualize and assess the cerebral microvasculature in vivo directly. Current technologies such as MRI are costly, may not be readily available in all communities, and thus may not be practical for routine screening and early detection of cognitive impairment.[9] Furthermore, typical MRI signs of cerebral small vessel disease, such as white matter hyperintensity (WMH) volume, are often nonspecific and present at later stages of small vessel damage.[10] Identification of a valid and reliable biomarker for alterations in the cerebral microvasculature would certainly be valuable in early detection, diagnosis, and monitoring disease progression in at-risk older adults and individuals with cognitive impairment.[11]

The brain and retinal vasculature share similar anatomic and physiologic features.[12,13] Alterations of retinal microstructure and microvasculature have been suggested to reflect similar changes occurring in the brain.[14] The retinal microvasculature has been used as a proxy in studying cerebral vascular abnormalities such as Alzheimer’s disease.[14] With the

recent advance of optical coherence tomography angiography (OCTA), direct visualization and further qualification of the retinal microvasculature is possible,[15] which provides a window to study the cerebral microvasculature. Wei et al. demonstrated the age-related decline of retinal blood flow velocity and microvessel density as well as intraretinal thickness in a group of the cognitively normal population.[15] The age-related thickness changes of the inner retina were also found to relate to the changes in retinal microvessel density during normal aging.[15] Similarly, Yu et al. reported decreased retinal vessel density and flow index with aging.[16]

There is accumulating evidence that cardiovascular fitness can reduce the impact of aging on cognitive function,[17–19] brain morphology[20,21] and cerebrovascular function.[22,23] Additionally, higher levels of cardiovascular fitness are associated with reduced cardiovascular risk, and therefore, increased cerebrovascular density.[24,25]

To our knowledge, however, no studies have examined the relationships among retinal vessel density, cardiovascular fitness, and cognitive function in presumed cognitively normal older adults. Therefore, the aim of this pilot study was to evaluate the relationships between retinal vessel density, physical performance, and cognitive function in older adults with no known cognitive function decline. We hypothesized that cognitive performance would be associated with (a) physical performance and (b) retinal vessel density.

METHODS

The Institutional Review Board for Human Research at the University of Miami approved the study. After a detailed description of the study was provided to each participant, they read and signed the approved written informed consent form. Healthy older subjects (age > 65 years) were recruited at the Department of Kinesiology and Sports Sciences at the University of Miami.

An ophthalmic examination was conducted by an ophthalmologist (HJ) to confirm eligibility. These examinations included best-corrected visual acuity, intraocular pressure (IOP), and a slit-lamp examination of anterior and posterior segments. Exclusion criteria included the presence of diagnosed dementia or MCI, refractive error greater than ± 6 diopters (D), obvious ocular media opacity, macular degeneration, and glaucoma. Other exclusion criteria were cardiovascular diseases or systemic diseases such as a history of stroke, coagulopathy, and uncontrolled hypertension and diabetes. A total of 20 eligible subjects were enrolled.

Both eyes of each subject were imaged using an OCTA device (AngioVue, Optovue, Inc., Fremont, CA, USA). The OCTA system is a spectral-domain optical coherence tomography system with a scan speed of 70,000 Å per second and an axial resolution of 5 μm. Retinal angiography and the corresponding tissue volume were obtained using the retinal 3 × 3 mm angiography scan protocol. The macula, centered on the fovea, was imaged. The image quality was set as ≥ 7/10 to ensure the acquisition of high-quality angiography. Angiographic images (i.e., en face view images) of the vascular slabs, including total retinal vascular network (RVN), superficial vascular plexus (SVP), and deep vascular plexus

(DVP), were created (Fig. 1).[26,27] The SVP includes the ganglion cell and inner plexiform layers, whereas the DVP consists of the inner nuclear and outer plexiform layers. RVN includes both SVP and DVP.

Image processing to measure the vessel density of these retinal vascular slabs has been reported in detail previously.[15] Briefly, the angiographs of the images were analyzed using fractal analysis. The box-counting method was used to yield the fractal dimension (Dbox), representing vessel density. The measurements included vessel density in RVN (RVD), in SVP (SVD), and in DVP (DVD).

Two commonly used brief screening tests were used to assess cognitive function: The mini-mental state examination (MMSE)[28] and Montreal Cognitive Assessment (MoCA).[29] The MMSE and MoCA both capture cognitive domains of memory, orientation, and construction, but the MoCA has additional visuospatial, executive, and language items and is more sensitive to mild cognitive impairments and reductions in cognitive function resulting from cerebrovascular abnormalities.[30] However, the MoCA may be more subject to educational biases, and scores are typically lower than MMSE when both are administered.[31,32] To account for this, an adjustment of 1 point is added to the overall score for individuals with ≤12 years of education.[33] Both tests were administered in a controlled environment immediately following completion of the health screening and informed consent documents. Participants were recruited based on self-reports of being cognitively normal with no prior diagnosis of mild cognitive impairment or dementia. The MMSE and MoCA were collected at baseline and used as continuous variables in analyses.

The YMCA submaximal cycle ergometer test was used to determine estimated peak oxygen consumption (VO_{2peak}).[34] This graded exercise test is designed with three-minute stages, with only very fit individuals completing three stages. Prior to the onset of testing, the test was explained to the subject, and seat and handlebar heights were adjusted to optimize each subject's mechanical advantage. Each participant began pedaling on a Monark cycle ergometer (Model 839E, Vansbro, Sweden) at 0.5 kg and 50 rpm (150 kpm-min^{-1}). Cadence was maintained by matching sound cues from a metronome. The resistance added at the beginning of each stage was dependent upon the subject's heart rate response during the first stage. Each stage of the test was performed at 50 rpm. If the participant's heart rate varied > 5 beats per minute between the last two minutes of each stage, an additional minute was added to that stage. This process was continued until a steady state was reached. If the subject was unable to maintain cadence, or if they were unable to reach a steady state, the test was concluded. Additionally, the test was terminated upon the participant's request. Two completed stages were required to calculate estimated VO_{2peak}; however, in the current study, eight participants were unable to complete two stages. Therefore, total work (TW-YMCA) was calculated and used to quantify the performance.[35] Total work was computed as the product of the distance traveled per pedal cycle (6 m), the cadence (50rpm), and the external load multiplied by the duration for each completed phase. The result was then converted to joules (J) by multiplying by 9.807 J·kg-m^{-1} and multiplied by 0.001 to convert J to kJ.

Descriptive statistics were obtained, and data analyses were conducted using an SPSS statistical software package (SPSS for Windows 25.0; SPSS Inc, Chicago, Illinois, USA). Shapiro-Wilk test of normality was used to test whether the data are normally distributed. As the MMSE was not normally distributed, we chose to use nonparametric Spearman correlations (r_s) to determine the relationships between MMSE, MoCA, TW-YMCA, and ocular variables. Exploratory analysis using partial correlations controlling for age, sex, education, and BMI was also performed to determine the relationships among vessel density, cognition tests, and cardiovascular performance. Significance was set *a* priori at $P < 0.05$.

RESULTS

Characteristics of the participants are presented in Table 1. There were no significant differences in any variable between female and male participants ($P > 0.05$), except for the height (159.7 cm vs. 173.9 cm, $P < 0.001$) and TW-YMCA (11.7 KJ vs. 22.8 KJ, $P = 0.04$). Tests of normality showed vessel densities and MoCA were normally distributed, while MMSE was not normally distributed.

The MoCA was significantly correlated to vessel density of SVD ($r_s = 0.53$, $P = 0.02$, Table 2) but not RVN ($r_s = 0.39$, $P = 0.09$) and DVP ($r_s = 0.02$, $P = 0.93$). MoCA was not correlated with TW-YMCA ($r_s = 0.05$, $P = 0.83$). Retinal microvascular densities were not related to TW-YMCA ($r_s = -0.05 \sim 0.18$, $P > 0.05$). Additionally, MMSE was not related the retinal vessel densities ($r_s = -0.10 \sim 0.21$, $P > 0.05$) and TW-YMCA ($r_s = - 0.19$, $P = 0.41$).

Analyses using partial correlations ($r_{partial}$) after controlling age, sex, education and BMI, revealed that the MoCA was significantly correlated to vessel density of RVN ($r_{partial} = 0.75$, $P = 0.001$) and SVP ($r_{partial} = 0.73$, $P = 0.001$), but not DVP ($r_{partial} = 0.11$, $P = 0.67$). MoCA was not related with TW–YMCA ($r_{partial} = 0.49$, $P = 0.06$). Retinal microvascular densities was not related to TW–YMCA ($r_{partial}= 0.04 \sim 0.49$, $P > 0.05$). Additionally, MMSE was not related to retinal vessel densities ($r_{partial} = -0.15 \sim 0.21$, $P > 0.05$) and TW-YMCA ($r_{partial} = -0.30$, $P = 0.27$).

DISCUSSION

To the best of our knowledge, this is the first study to reveal the positive correlation between retinal microvascular density and MoCA score in cognitively normal older adults without a diagnosis of mild cognitive impairment (MCI) or dementia. This result suggests that retinal microvascular changes could be further developed into a simple and cost-effective marker for evaluating the vascular contributions to cognitive impairment and dementia (VCID). Previous studies have explored the relations between retinal microvasculature and cognition in patients with Alzheimer's disease (AD), and MCI (Table 3),[36–40] and retinal vessel density were found to be positively related to MoCA in patients with AD and MCI,[40] and MMSE in patients with AD.[36] However, other studies did not support the correlations between retinal vessel density and MMSE in patients with AD[38,39,41] or in patients with MCI.[37] Few studies have looked solely at cognitively normal older adults. Dissimilarities in study cohorts, imaging techniques, and sample sizes may have contributed to the differences in findings among studies.[36–40] The present study adds new information to the field by

establishing the relationship between retinal microvascular network density and cognitive performance in cognitively normal older adults.

Both MMSE and MoCA were used in the present study, but only MoCA showed correlations with retinal microvascular network density. This could be attributed to the greater range of cognitive domains testing in the MoCA, including executive, visuospatial, language, and attention tasks,[42,43] while the MMSE has an over-representation of orientation questions (i.e., 10 of 30 points) that may not reflect early cognitive changes. We chose to use the MMSE and MoCA in this study because both are often used in clinical practice as quick screening tools for patients with memory complaints.[44] The MoCA may provide higher classification accuracy than the MMSE in differentiating MCI from normal age-related changes.[44] Moreover, the MoCA has been used to reliably detect cognitive changes in MCI over a 3.5 years period, whereas MMSE could not.[45] The MoCA has also been reported to be impacted by age, education, and physical activity in healthy older adults.[46]

The TW-YMCA was used to evaluate the individual fitness levels in this group of cognitively normal older adults.[35] The results showed a trend toward a correlation between MoCA and TW-YMCA but did not reach a significant level. In addition, the TW-YMCA did not correlate with retinal vessel density, although in other studies, fitness levels (measured as running speed) were found to correlate to retinal vessel density determined by the size of the foveal avascular zone in young, healthy adults.[47] The lack of correlations between TW-YMCA and retinal vessel densities in the participants enrolled in the current study may be due to the small sample size and the non-homogeneous nature of the sample with respect to physical fitness levels. Several of the participants engaged in daily exercise, whereas others had a sedentary lifestyle. Future large sample studies may reveal the relationships between physical performance and retinal vessel densities in older adults, and especially when using less challenging cardiovascular assessments, like the six-minute walk test, which has previously been used in subjects with MCI.[48] Alternatively, baseline activity levels could be measured with a patient-reported outcome such as the Quick Physical Activity Rating to be used as a covariate.[49]

The correlation between retinal microvasculature and the MoCA scores found in the present study may suggest a potential link between the microvasculature of the retina and brain. Decreased retinal microvascular network density has been reported to be correlated with the Fazekas scale of brain white matter.[50] Moreover, Lee et al. recently reported that the density of peripapillary microvascular network was positively correlated with brain cerebral small vessel disease (CSVD) score assessed using 3D brain magnetic resonance imaging (MRI) in patients with subcortical vascular-related cognitive impairment (SCVI).[51] CSVD markers such as lacunas, white matter hyperintensity (WMH), and microbleeds are the hallmarks of vascular dementia.[52] Hence, the loss of the retinal microvascular network appears to reflect cerebral hypoperfusion in patients with both AD and MCI,[53–55] which may also be due to aging and other vascular risk factors.[7,8,56,57] Wei et al. demonstrated the decline of retinal vasculature in aged compared to young people.[15] Further, similar rates of decline were seen in RVN, SVP, and DVP vessel density (−0.03% to −0.08%) in a subgroup with the age of 35 years or older.[58] It has also been shown that the decline rate of retinal vessel density (−0.44% per year in DVP, normalized by tissue volume)[58] was about the same as

the decline rate in cerebral blood flow (−0.38 to −0.47% per year).[59,60] It is worth noting that the annular rate was analyzed in a cohort with a wide age range (≥ 35 years), and the comparison of the comparative rates in the retina and brain were derived from different studies with dissimilar cohorts.[58–60] Future studies incorporating simultaneous measures of cerebral and retinal microvascular alterations with aging may provide more accurate information on this topic. Nevertheless, it can be speculated that the decreased retinal microvascular density due to normal aging in the older adult cohort in the present study may reflect cerebral vascular changes. Additionally, the lack of association between retinal vessel density in DVP and cognition in the present study may have been due to the narrow age range and the small size of our sample. Further studies with large sample sizes and a wider age range may validate the position.

There are several limitations to this study. First, the sample size was small, which limited the ability to detect small effect sizes. As a pilot study, this work permits hypothesis generation for a larger study.[24,28] Second, we did not study cerebral vasculature. Future studies should simultaneously study both the retinal and cerebral microvascular differences due to aging or fitness levels or changes due to specific interventions such as exercise to help establish the retinal microvascular network as a proxy in monitoring cognitive changes in older adults. Third, we focused on cognitively normal older people and did not include patients with diagnoses of cognitive impairment, although previous studies reported the retinal microvascular alterations in such patients. Three individuals had MoCA scores below the recommended cut-off of 26, suggesting they could have MCI. However, these individuals self-reported no cognitive impairment, had no diagnosis of MCI or dementia, were functionally independent, had normal MMSE, and although they had the lowest MoCA scores, also had the lowest educational attainment in the cohort (12, 14, and 16 years). These factors support the classification of these individuals as cognitively normal. Fourth, our cognitive assessment in this pilot was limited to brief, commonly used screening tests (MoCA and MMSE). Future studies should include a more detailed cognitive assessment. Fourth, when assessing correlations between physical fitness, cognitive performance, and retinal microvasculature, long-term training studies would produce a clearer picture of these relationships. Last, we employed the TW-YMCA as a marker of cardiovascular fitness rather than employing peak oxygen consumption tests (VO_{2peak}).

In summary, this pilot study provides some of the first evidence that retinal microvasculature, measured as the retinal microvascular network density, was positively related to cognition, as determined by the MoCA. This relationship provides evidence that evaluation of microvasculature in the retina could be further developed into a viable and cost-effective tool for examining the contribution of vascular changes to age-related cognitive deficits.

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Highlights

- The densities of retinal vessels were measured in older people.
- Cognitive function was also measured.
- The vessel density was correlated with the cognitive function measured with MoCA.

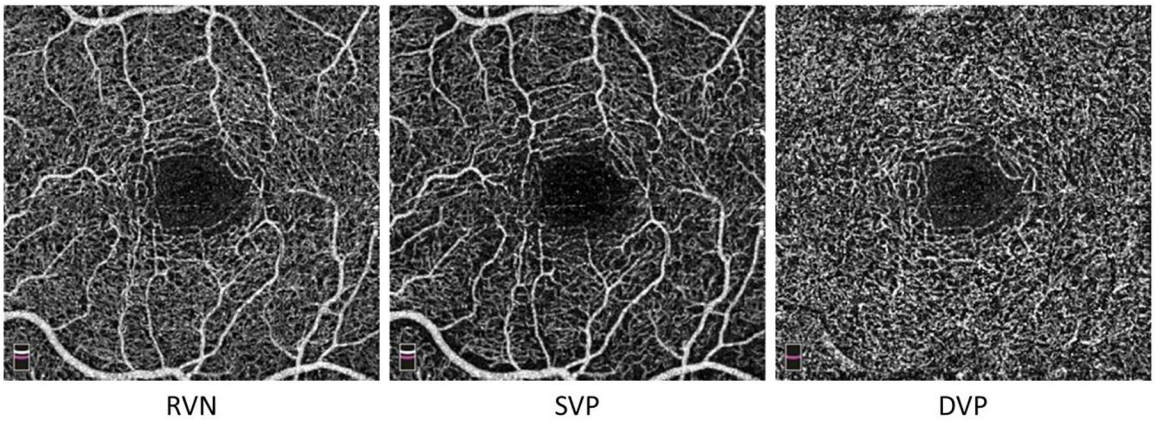

Figure 1. OCTA enface images.

A study subject was scanned at the macula centered on the fovea (i.e., central area with no vessels) with a field of view 3 × 3 mm. Angiographic images (i.e., enface view images) of the vascular slabs, including total retinal vascular network (RVN), superficial vascular plexus (SVP), and deep vascular plexus (DVP), show capillary network around the avascular fovea. Note, there is only the capillary network in the DVP slab, in contrast to RVN and SVP, which mixed capillary network with small vessels (i.e., arterioles and venules).

Table 1:

Sample Characteristics

Variable	Mean (SD) or %	Range
Age, y	71.2 (5.3)	63–83
Education, y	16.5 (2.0)	12–22
Sex, %F	55.0	
Body Mass Index (kg/m^2)	29.0 (6.3)	20.6–43.5
Hypertension, %	50.0	
Dyslipidemia, %	55.0	
Heart Disease, %	20.0	
Alcohol Use, %	15.0	
SBP (mmHg)	134 (20)	101–171
DBP (mmHg)	79 (10)	55–97
HR (beat / min)	63 (12)	43–84
IOP (mmHg)	16.6 (2.8)	10.5–20.5
MAP (mmHg)	97 (11)	70.3–116.3
MOPP (mmHg)	54 (6)	38.6–64.2
TW-YMCA (KJ)	16.6 (9.2)	4.4–35.3
MoCA	27.6 (1.9)	23–30
MMSE	29.7 (0.6)	28–30
Mean RVD	1.79 (0.01)	1.78–1.81
Mean SVD	1.78 (0.19)	1.73–1.81
Mean DVD	1.80 (0.01)	1.79–1.81

KEY: SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; IOP = intraocular pressure; MAP = mean arterial pressure; MOPP = mean ocular perfusion pressure; TW-YMCA = Total Work on the YMCA Ergometer; MoCA = Montreal Cognitive Assessment; MMSE = Mini Mental State Examination; RVD = vessel density in retinal vascular network; SVD = vessel density in superficial vascular plexus; DVD = vessel density in deep vascular plexus.

Table 2:

Correlation and Partial Correlations Between Cognitive and Physical Performance and OCTA Measures

Spearman Correlation			
Variable	**MoCA**	**MMSE**	**TW-YMCA**
TW-YMCA	0.05 (0.83)	−0.19 (0.41)	1
Mean RVD	0.39 (0.09)	0.21 (0.37)	0.18 (0.49)
Mean SVD	**0.53 (0.02)**	−0.10 (0.67)	−0.15 (0.52)
Mean DVD	0.02 (0.93)	0.12 (0.63)	−0.05 (0.84)
Partial Correlations (adjusted for age, sex, education, BMI)			
Variable	**MoCA**	**MMSE**	**TW-YMCA**
TW-YMCA	0.49 (0.06)	−0.30 (0.27)	1
Mean RVD	**0.75 (0.001)**	0.21 (0.43)	0.47 (0.07)
Mean SVD	**0.73 (0.001)**	0.00 (0.99)	0.49 (0.05)
Mean DVD	0.11 (0.67)	−0.15 (0.58)	0.04 (0.89)

Correlation coefficient (p-value); **Bold** signifies significance after correction for multiple comparisons. KEY: TW-YMCA = Total Work on the YMCA Ergometer; MoCA=Montreal Cognitive Assessment; MMSE = Mini Mental State Examination; RVD = vessel density in retinal vascular network; SVD = vessel density in superficial vascular plexus; DVD = vessel density in deep vascular plexus.

Table 3.

Retinal microvasculature and cognition in previous studies

Study	Sample	Age (year)	Cognition	OCTA parameters	Correlation (r)
Present Study	20 cognitively normal older adults	71.0 ± 5.4	MoCA	RVD SVD DVD	RVD, r_s = 0.37, P = 0.02 SVD, r_s = 0.60, P < 0.001
Criscuolo et al. 2018[37]	27 aMCI	73 ± 6	MMSE	SCP, DCP, RPC, FAZ	No association
Zabel et al. 2019[39]	27 AD	74.1 ± 5.9	MMSE	DVD, SVD, FAZ	No correlation
Lahme et al. 2018[38]	36 AD	68.0 ± 9.3	MMSE	FD	No correlation
Zhang et al. 2019[40]	3 eAD 13 aMCI	73.0 ± 8.2	MoCA	SVD, peripapillary RPC VLD	SVD, r = 0.36, P = 0.043, PRC VLD, r = 0.46, P = 0.01
Bulut et al. 2018[36]	26 ATD	74.2 ± 7.6	MMSE	VD FAZ	VD, r = 0.438, P = 0.001 FAZ, r = −0.531, P < 0.001
Wang et al. 2021[41]	62 AD, 47 MCI, and 49 HC	74.2 ± 7.6	MMSE Fazekas score	VD	No correlation

MoCA: Montreal cognitive assessment; RVD: vessel density in the retinal vascular network; SVD: vessel density in the superficial vessel plexus; aMCI: Amnestic Mild Cognitive Impairment; MMSE: the Mini-Mental State Examination test; SCP: superficial capillary plexus; DCP: deep capillary plexus; RPC: radial peripapillary capillary; FAZ fovea avascular zone; AD: Alzheimer's Disease; MCI: mild cognitive impairment; HC: healthy control; DVD: vessel density in deep retinal vascular plexus; FD: flow density; eAD: early Alzheimer's Disease; RPC VLD: radial peripapillary capillary vessel length density; ATD: Alzheimer's type dementia; VD: vessel density.