Brief Report

Association Between Optical Coherence Tomography Angiography (OCTA)-Based Retinal Vascular Densities and Empathy in Young Adult

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Association Between Optical Coherence Tomography Angiography (OCTA)-Based Retinal Vascular Densities and Empathy in Young Adults

Bess Yin-Hung Lam [1,*], Carole Leung [2], Ka-Shun Lei [2], Kaiyip Choi [3] and Henry H.L. Chan [3]

[1] Department of Counselling and Psychology, Hong Kong Shue Yan University
[2] Faculty of Health and Social Sciences, Hong Kong Polytechnic University
[3] School of Optometry, Hong Kong Polytechnic University
* Correspondence: bess0127@gmail.com

Abstract

With the use of Optical Coherence Tomography Angiography (OCTA), the present study is the first study to examine if retinal vascular densities (vessel densities and perfusion densities) could be associated with empathetic levels in young adults. **Methods:** Fifty-one university students aged from 18 to 25 years (26 males and 24 females) were recruited from a university in Hong Kong. OCTA was conducted to assess their retinal vessel density (VD) and perfusion density (PD) in different scan patterns over the macula (1 mm center subfield, 3x3 mm scan, 6x6 mm scan). Empathy (cognitive, affective, and somatic) was measured by using the Cognitive, Affective, and Somatic Empathy Scales (CASES). **Results:** After controlling for age, the multiple linear regression results showed that both the VD and PD in the 1 mm center subfield were significantly and negatively associated with the empathy total score, the affective empathy subscore, and the somatic empathy subscore, respectively (*ps* < 0.05). **Conclusion:** The present findings indicate that a lower level of empathy is associated with the retinal vascular densities in the 1 mm center subfield, including higher VD and PD, in healthy individuals, setting the foundation for futures studies investigating the underlying mechanism of retinal imaging and empathy.

Keywords: empathy; Optical Coherence Tomography Angiography; retinal vessel; perfusion; biomarkers

1. Introduction

Empathy is the social cognitive ability to understand and share another person's feelings [1]. Empathy im-pairment is also associated with schizophrenia [2]. Previous literature focused on brain imaging studies to examine individuals with these problems [3,4] while the retinal findings were scarce. This study explored whether empa-thetic problems could be delineated by the approach of retinal imaging which has a close linkage with brain imaging.

London, Benhar, and Schwartz [5] described "the retina as a window to the brain." The retina is an extension of the central nervous system and its physical structures and functions are similar or closely related to the brain. For instance, brain imaging abnor-malities (e.g., white matter lesions, atrophy) and small cerebral artery changes were found to be significantly related to retinal microvascular changes [6]. With regard to the relationship among retinal vessel density (VD), perfusion density (PD), vessel diameter, and retinal nerve fiber layer (RNFL), Geneid et al. [7] found that the narrower the retinal vessels' diameter (both arteriolar and venular diameters), the thinner the RNFL. These findings suggest that retina VD, PD, vessel diameter, and RNFL are closely related to each other.

With the advancement of retinal imaging techniques such as Optical Coherence Tomography Angiography (OCTA), more ophthalmic studies have been conducted to investigate how the changes

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in the eyes are associated with psychological functioning and cognitive functioning in recent years [6,8]. However, little is known about whether retinal microvascular changes are related to empathy, which is closely associated with cognitive function [1]. The present study aimed to examine the relationship between retinal vascular densities, vessel densities (VDs), and perfusion densities (PDs) and em-pathy in non-clinical young adults. It was hypothesized that VD and PD would be asso-ciated with empathy.

2. Materials and Methods

2.1. Participants

The study was approved by the University Human Subjects Ethics Sub-committee. Fifty-one healthy university students took part in the study and the mean age of the participants was 21.33 (SD = 1.40) (26 males, 51%). One participant did not disclose his or her gender. All the healthy participants met a number of inclusion criteria in this study: 1) participants aged between 18 and 25, 2) had good corrected visual acuity, 3) had satis-factory general and ocular health, 4) had no history of retinal vascular pathologies, and 5) were not diagnosed with any psychiatric disorders nor were they undergoing psychiatric medication. Those who reported any history of retinal vascular pathologies were ex-cluded from this study.

2.2. Procedures

Written informed consent was obtained from all the participants. Before the administration of the pupil dilation drug, eye assessments of habitual distant visual acuity, intraocular pressure, and the anterior parts (e.g., the cornea) of each eye were conducted. Then, a registered optometrist placed a drop of Mydrin-P (0.5% Tropicamide + 0.5% Phenylephrine) in each eye for dilated fundus examination. The pupil dilation period lasted around 15 to 20 minutes. Upon the confirmation of the pupil dilation size by the optometrist, 6 mm x 6 mm retinal scans of angiography images were captured from both eyes over the macula via optical coherence tomography angiography (OCTA) (Zeiss CIRRUS HD-OCT 5000, Carl Zeiss Meditec, Inc., Dublin, USA) in a dark room. The participants' retinal blood VD and PD were measured and analyzed according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grid using Zeiss AngioPlex (Carl Zeiss Meditec, Inc., Dublin, USA). The VD and PD measures for analysis were the 1 mm center subfield, 3x3 mm scan pattern, and 6x6 mm scan pattern. The participants also filled in the Cognitive, Affective, and Somatic Empathy Scales (CASES) [1].

2.3. Measures

2.3.1. OCTA: VD and PD

Five indexes (vessel area density (aka perfusion density), vessel skeleton density (aka vessel density), vessel diameter index, vessel perimeter index, and vessel complexity index) can be used to objectively analyze retinal vascular abnormalities from OCT angiogram (OCTA) scans. [9] VD is defined as the ratio of the total length of the blood vessels to the total image area of a region of measurement [9]. PD represents the ratio of the total area occupied by blood vessels to the total image area in a region of measurement [9].

Three commonly used OCTA scan patterns were acquired using an ETDRS grid, which includes the 1 mm center subfield, 3x3 mm scan pattern, and 6x6 mm scan pattern. Densities from the left eye and the right eye were summated for analysis in all the scan patterns. The densities of the four quadrants (superior, nasal, temporal, and inferior quadrant) were also computed for each of the following scan patterns: 3x3 mm scan, 6x6 mm scan (Figure 1).

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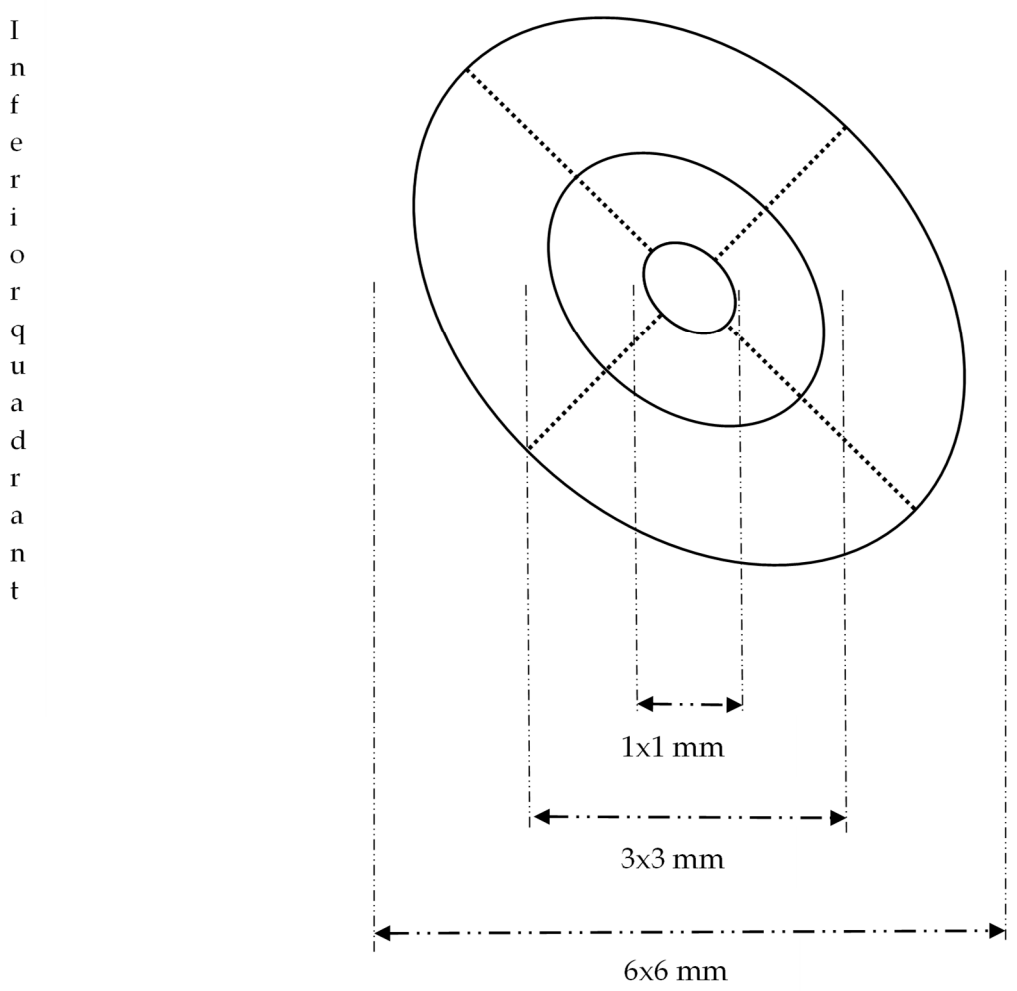

Figure 1. *A Diagram of the OCTA Scan Patterns. Note*. This is a diagram showing the Early Treatment Diabetic Retinopathy Study (ETDRS) grid region overlay used for calculating the retinal vessel density (VD) and perfusion density (PD) in the 1x1 mm center subfield, 3x3 mm scan pattern, and 6x6 mm scan pattern.

2.3.2. Cognitive, Affective, and Somatic Empathy Scales (CASES)

Empathy was measured via CASES [1] with a three-factor structure (cognitive empathy, affective empathy, and somatic empathy). Cognitive empathy refers to the ability to understand others' feelings. Affective empathy refers to the ability to perceive others' feelings. Somatic empathy refers to the automatic bodily response to an observed event. A lower score on the scales suggests that the participant has a deficit in empathic abilities.

2.3.3. Statistical Analysis

A summation of the VD and PD measures from both eyes and the four quadrants were computed. In order to test whether retinal vascular densities were associated with the level of empathy among young adults, multiple linear regression analyses were conducted. The dependent variable for all the regression analyses was empathy. The regression analyses were conducted separately for each retinal measures paired with each CASES score.

 doi:10.20944/preprints202507.1314.v1

3. Results

3.1. Descriptive Statistics

The mean age was 21. 33 years (S.D.= 1.40 years). The means of empathy (CASES) total, cognitive, affective, and somatic scores were 36.56, 12.76, 12.84, and 10.82, respectively (Table 1). With regard to the retinal vascular densities (VDs), the means of the 1 mm center subfield, 3x3 mm scan pattern and 6x6 mm scan pattern were 20.41 (S.D.= 4.94), 146.62 (S.D.= 8.12), and 150.76 (S.D.= 5.35). Regarding the PD estimates, the means of the 1 mm center subfield, 3x3 mm scan pattern and 6x6 mm scan pattern were 0.45 (S.D.= 0.11), 3.46 (S.D.= 0.20), and 3.70 (S.D.= 0.12).

Table 1. Descriptive Statistics of All the Variables in the Present Study.

Variables		***Mean***	***SD***
CASES (empathy scores)	Total score (Range= 9- 58)	36.56	9.95
	Cognitive score	12.76	3.70
	Affective score	12.84	3.79
	Somatic score	10.82	3.78
Retinal vascular densities	VD in the 1 mm center subfield	20.41	4.94
	VD in the 3x3 mm scan pattern	146.62	8.12
	VD in the 6x6 mm scan pattern	150.76	5.35
	PD in the 1 mm center subfield	0.45	0.11
	PD in the 3x3 mm scan pattern	3.46	0.20
	PD in the 6x6 mm scan pattern	3.70	0.12
Age		21.33	1.40

Note. VD, vessel density; PD, perfusion density; CASES, Cognitive, Affective, and Somatic Empathy Scales; SD, standard deviation.

3.2. Correlations and Regression Analyses

Significant negative correlations were found between the VD and PD in the 1 mm center subfield and CASES-total score, affective score, and somatic score (range of r = -.34 to -.30, ps < .05) (Table 2).

After controlling for age, the CASES-total score was significantly and negatively associated with VD in the 1 mm center subfield (R^2 = .16, F(2,47) = 4.46, p = .02, β = -.28, t(47) = -2.12, p = .04) and PD in the same region (R^2 = .17, F(2,47) = 4.65, p = .01, β = -.29, t(47) = -2.20, p = .03). The results for the relationship between VD and PD in 3x3 mm and 6x6 mm scan patterns were not significant (ps > .05). In terms of the three empathy subscores, significant results were found for the VD and PD measures in the 1 mm center subfield in relation to CASES-affective and CASES-somatic empathy (ps < .05). Specifically, the VD and PD in the 1 mm center subfield were significant predictors of the CASES-affective score (VD: R^2 = .13, F(2,47) = 3.42, p = .04, β = -.30, t(47) = -2.19, p = .03; PD: R^2 = .13, F(2,47) = 3.42, p = .04, β = -.30, t(47) = -2.19, p = .03). The CASES-somatic score was significantly and negatively associated with VD in the 1 mm center subfield (R^2 = .14, F(2,48) = 4.03, p = .02, β = -.32, t(48) = -2.35, p = .02) and PD in the same region (R^2 = .15, F(2,48) = 4.30, p = .02, β = -.33, t(48) = -2.46, p = .02). With the significance threshold after the Bonferroni correction (p< 0.025), all these results became marginally significant.

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Table 2. Correlations between the Variables in the Present Study.

	Major variables	1	2	3	4	5	6	7	8	9	10	11
1.	Age	1	-	-	-	-	-	-	-	-	-	-
2.	VD in the 1 mm center subfield	-.06	1	-	-	-	-	-	-	-	-	-
3.	VD in the 3x3 mm scan pattern	-.03	.51***	1	-	-	-	-	-	-	-	-
4.	VD in the 6x6 mm scan pattern	.15	.25	.67***	1	-	-	-	-	-	-	-
5.	PD in the 1 mm center subfield	-.05	.995***	.54***	.27	1	-	-	-	-	-	-
6.	PD in the 3x3 mm scan pattern	-.10	.48***	.98***	.64***	.51***	1	-	-	-	-	-
7.	PD in the 6x6 mm scan pattern	.09	.15	.69***	.72***	.20	.71***	1	-	-	-	-
8.	CASES-Total	.28*	-.30*	-.15	-.14	-.30*	-.12	-.07	1	-	-	-
9.	CASES-Cognitive	.28*	-.13	-.03	-.02	-.14	-.01	.01	.83***	1	-	-
10.	CASES-Affective	.20	-.31*	-.16	-.19	-.31*	-.14	-.09	.91***	.61***	1	-
11.	CASES-Somatic	.21	-.33*	-.17	-.16	-.34*	-.15	-.09	.90***	.60***	.79***	1

Note. *$p < .05$, ** $p < .01$, *** $p < .001$.; VD, vessel density; PD, perfusion density; CASES, Cognitive, Affective, and Somatic Empathy Scales.

4. Discussion

To the authors' best knowledge, the current study was the first to examine the relationship between retinal vascular densities (vessel densities and perfusion densities) and empathetic levels in healthy young adults. The VD and PD in the 1 mm center subfield over the macula were negatively associated with the affective empathy and somatic empathy levels. The present findings not only set the scientific foundation for investigating the relationship between retinal characteristics and empathy in the field; they also suggest that retinal microvascular abnormality can potentially be used as a biomarker for the detection of those with a lack of empathy.

A significant relationship between retinal vasculature and empathy found in the present study supports the notion that retinal microvasculature is closely related to empathy. Specifically, the current results show that both the VD and PD in the 1 mm center subfield were significantly and negatively associated with the empathy total score, the affective empathy subscore, and the somatic empathy subscore, respectively. Indeed, previous findings suggested that wider retinal venules were found associated with more psychosis symptoms during childhood with a higher likelihood to experience psychosis symptoms during adulthood [10]. This might be because an insufficient supply of oxygen to the brain can also lead to the dilation of retinal venules [11], suggesting a close relationship between the brain and the retina and also the potential inverse relationship between wider vessels and empathy. Furthermore, conditions associated with increased retinal vascularization, such as inflammation [12], may negatively affect brain areas responsible for empathy, leading to a decrease in empathetic responses. Although the current finding on the relationship between retinal vascular densities and empathy was based on a non-clinical sample, the result aligned with what was found in previous ophthalmic research [8] on schizophrenia patients and people who have high trait anger and are impaired in regard to empathetic skills. More importantly, the present findings extend the previous literature on the relationship between cognitive function and retinal characteristics by establishing the relationship between empathy (affective and

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somatic empathy) and specific retinal microvascular characteristics (the VD and PD in the 1 mm center subfield).

There are several possible explanations underlying the relationship between PD and VD and empathy (affective and somatic empathy) found in the current sample. Specifically an insufficient supply of oxygen to the brain and retina tissues or structural damage due to inflammation or endothelial dysfunction may negatively impact social cognitive functioning and emotional responses [10,11]. For instance, the retinal vascular changes detected by OCTA could be a reflection of social cognitive changes resulting due to structural alterations in the brain. This might explain the significant association between retinal characteristics and empathy levels. However, it is important to note that the retinal characteristics were not found to be significantly associated with cognitive empathy. This may be due to the fact that cognitive empathy is more influenced by age, rather than by retinal vasculatures which was supported by our current data, which is consistent with Del Rey et al.'s [13] finding.

Limitations

There are a number of limitations that should be addressed in future studies. For instance, the underlying mechanism of the relationship between retinal vasculature and empathy is yet to be investigated. Future studies should also administer neuroimaging methods to investigate brain structural change and cerebral blood flow information in order to help gain a better understanding of how the retina acts as a window to the brain in relation to empathy.

5. Conclusions

These key findings indicate that retinal microvascular abnormality might potentially be used as a biomarker for the detection of those with a lack of empathy including schizophrenia. Although more precise segmentation of different layers in the fundus is provided by OCTA when compared with FA, it is noteworthy that the combinatorial approaches of OCTA and FA could be more accurate in detecting those with a lack of empathy in a clinical setting.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1: title; Table S1: title; Video S1: title.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data is available upon request.

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Abbreviations

The following abbreviations are used in this manuscript:

MDPI	Multidisciplinary Digital Publishing Institute
DOAJ	Directory of open access journals
TLA	Three letter acronym
LD	Linear dichroism

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