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Altered macular microvasculature in Neuromyelitis Optica Spectrum Disorders


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Abstract

**Purpose:** To evaluate macular microvascular changes in neuromyelitis optica spectrum disorders (NMOSD) by using optical coherence tomography angiography (OCT-A) and investigate their correlations with neuroaxonal structural damage evaluated with Spectral domain OCT (SD-OCT).

**Design:** Cross-sectional study.

**Methods:** Twenty eyes of 20 patients with NMOSD and 21 eyes from 21 healthy controls were enrolled. OCT-A was used to obtain microvascular network images of the whole, superficial, and deep retinal capillary plexuses (WRCP, SRCP, and DRCP) in a 3-mm diameter area around the macula. Spectral domain OCT was used to obtain the intra-retinal thickness. Custom automated algorithms quantified the thickness of the intra-retinal layers as well as microvascular density of the retinal capillary layers.

**Results:** NMOSD patients showed significantly decreased microvascular density in both SRCP and DRCP (P < 0.05) compared to controls. The decreased microvascular density in SRCP and DRCP significantly correlated with the frequency of ON attack (P <0.05). Both SRCP and DRCP microvascular density significantly correlated (P<0.05) with retinal nerve fiber layer (RNFL) and ganglion cell layer with inner plexiform layer (GCIP). SRCP microvascular density moderately correlated with visual acuity, while a stronger correlation was found between DRCP and visual acuity.

**Conclusions:** Decreased microvascular density in NMOSD patients correlated with the worsening of their visual acuity. Correlation between microvascular impairment and neuroaxonal thinning revealed retinal microvascular alteration may contribute to neuroaxonal loss in NMOSD patients. OCT-A with measurable analysis offers a new path of study and will likely be useful as an objective biomarker for detecting microvascular impairment in NMOSD.
Title Page

Altered macular microvasculature in Neuromyelitis Optica Spectrum Disorders

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Author names, degrees, and affiliations:

William Robert Kwapong¹, M.D., Chenlei Peng¹, M.D., Zhiyong He², M.D, Xiran Zhuang¹, M.D.,
Meixiao Shen¹, Ph.D., Fan Lu¹, M.D, Ph.D.
¹School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, Zhejiang, China.
²The 2nd Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Wenzhou,
Zhejiang, China.

Corresponding Authors:

Meixiao Shen, Ph.D. & Fan Lu, MD, Ph.D.

Mailing address: School of Ophthalmology and Optometry, Wenzhou Medical University, 270 Xueyuan
Road, Wenzhou, Zhejiang, China, 325027.

Tel: (086) 577-88824116; Fax: (086) 577-88824115

Email: lufan62@mail.eye.ac.cn; shenmxiao7@hotmail.com


Introduction

Neuromyelitis optica spectrum disorders (NMOSDs) are rare but severe relapsing inflammatory demyelinating disorders\(^1\) characterized by devastating optic neuritis (ON) as its hallmark. The optic neuritis in NMOSD causes neuroaxonal damage to the optic nerve and retina which leads to impairment of vision\(^2\).

With the use of the optical coherence tomography (OCT), thinning of the peripapillary retinal nerve fiber layer (pRNFL)\(^3-7\) has been increasingly recognized as a marker for the neuroaxonal damage and has been shown to correlate with the visual dysfunction\(^8\). Previous articles have also found that degeneration occurs in the RNFL, inner retina\(^8,9\) and some layers of the outer retina\(^10\). Blood vessels within the retina contribute to the retinal thickness and could present as an important cofounder in the pathogenesis of NMOSD in the retina.

Few literature\(^11,12\) have reported on the vascular changes that occur in the retina due to insufficient imaging modalities. Optical coherence tomography angiography (OCT-A) is a new imaging modality based on the OCT technology used to characterize the three-dimensional vasculature in various retinal layers and provides quantitative assessment of the microvascular and morphologic structure in the retina. The current study was performed to evaluate the macular microvascular changes in neuromyelitis optica spectrum disorders (NMOSD) by using OCT-A and investigate their correlations with neuroaxonal structural damage evaluated with Spectral domain OCT (SD-OCT), as well as visual acuity (VA).

Materials and Methods

Study design

This is a cross-sectional study. Ethical approval for the study was obtained from the institutional Ethics Committee and written informed consent was obtained from each participant in accordance with Declaration of Helsinki.

Patient selection

Twenty patients with NMOSD were enrolled from the Second Affiliated Hospital, Wenzhou Medical University, Wenzhou, China. The patients enrolled were diagnosed with NMOSD by a single neurologist (Zhiyong He, MD) based on the revised diagnostic criteria of Wingerchuk\(^13\). 21 healthy individuals who were matched for age and gender with NMOSD patients were included as controls. NMOSD patients and controls with known ophthalmological disease (glaucoma, cataract, high myopia, amblyopia et al) and with known systematic/neurological disease (diabetes, multiple sclerosis, et al) were excluded. NMOSD patients with ON within the previous 6 months were excluded. Any individual with previous ocular
surgery that could affect the visual outcomes or the macular morphology was also excluded from the study.

Macular capillary plexus imaged by OCT-A and quantitative analysis

Retinal microvasculature around macula was imaged by the RTVue XR Avanti Spectral Domain OCT (SD-OCT) system (Optovue, Inc., Fremont, CA) equipped with AngioVue software (Version 2015.1.0.90). The scan speed was 70,000 A-scans per second and the scan area, centered on the fovea was 3 × 3 mm², obtained by orthogonal registration and merging of two consecutive scans. The size of the exported OCT-A images was 304 × 304 pixels. The eye movement was offset during image processing using the Motion Correction Technology (MCT) function. A good set of scans, with a signal strength index (SSI) of > 40 for each eye, was selected for further analysis. Any image with double vessel pattern or motion artifacts more than three lines was excluded. The superficial, deep and whole retinal capillary plexuses were imaged and separated automatically by the instrument. The superficial retinal capillary plexus (SRCP) extended from 3µm below the internal limiting membrane to 15µm below the inner plexiform layer (IPL) and the deep retinal capillary plexus (DRCP) extended from 15 to 70 µm below the IPL. The whole retinal capillary plexus (WRCP) was segmented from 3 µm beneath the ILM to 30 µm beneath the retinal pigment epithelium (RPE) layer, according to the manufacturer’s instructions.

A custom automated algorithm was performed on the en face OCT-A projection images to quantify the microvascular density at the levels of the SRCP, DRCP and WRCP, which has been described in detail in our published studies. Briefly, the grayscale of each two-dimensional OCT-A image was extended by bicubic interpolation to 1024×1024 pixels to enhance the image details. Then, the image was segmented to obtain the microvascular network. First, the boundary foveal avascular zone (FAZ) was detected by using a two-way combined method consisting of a canny edge detector algorithm and a level set algorithm. The area within the FAZ having a circle of fixed radius (diameter = 0.6 mm) was then determined to establish the baseline signal-to-noise ratio for the global thresholding. The image was then processed separately to generate two binary images. The first one contained only the large blood vessels and was generated by using global thresholding, a local gray-level change enhancement algorithm called “gray-voting”, Gabor filtering, and adaptive thresholding. The other binary image contained the large and small vessels and was created by using global thresholding, gray-voting algorithm, and adaptive thresholding. Lastly, the two resulting binary vessel maps were subtracted to obtain the binary image containing only the small vessels (capillaries). Based on the final binary image, an image is created by detecting the central axis of the binary, white-pixelated vasculature and remaining one pixel along the central axis.
Similar to our previously published studies\textsuperscript{15,16}, three forms of the analyzed regions were used to describe the density of the retinal microvasculature. First, the microvascular density was calculated for the 2.5 mm-diameter total annular zone after excluding the FAZ (diameter = 0.6 mm). The density was then calculated in three concentric isometric annular rings after excluding the FAZ (C1–C3). The density was also calculated in the parafoveal quadrant sectors, i.e., superior (S), temporal (T), inferior (I), and nasal (N) sectors of the 2.5-mm diameter circular zone after excluding the FAZ. The methods above were implemented using MATLAB v7.10 (Mathworks, Inc., Natick, MA, USA) and shown as a supplemental Figure 1. Bennett’s formula was used to correct the changes in axial length\textsuperscript{20,21}.

**Individual retinal layer thickness measured with SD-OCT**

A custom-built SD-OCT instrument with an ultra-high resolution of approximately 3\textmu m was used to image the macula. All the measurements were performed by a single, well-trained examiner. Radial scanning mode with 12 lines was applied to get three-dimensional (3D) OCT data. Upon data collection, SD-OCT images were processed automatically by using custom software, which was described in detail in our previous published papers\textsuperscript{22,23}. The software segmented the structures into 6 individual retinal layers (RNFL: retinal nerve fiber layer; GCIPL: ganglion cell-inner plexiform layer; INL: inner nuclear layer; OPL: outer plexiform layer; HFL+ONL: Henle fiber layer and outer nuclear layer; ORL: outer retinal layer, which consists of the inner segment and outer segment of the photoreceptors and the retinal pigment epithelium) and the total retinal layer (shown as a supplemental Figure 2). For each eye included in this study, 3D thickness map of each individual retinal layer was obtained based on the segmented layers. For analysis, the macular thickness map was divided into 9 sectors, and it was displayed as 3 concentric circles, including a central circular subfield (1 mm diameter) and an inner ring (1 to 3 mm diameter), and an external ring (3 to 6 mm diameter), with each ring divided into 4 quadrants. Nine sectors included: central region (C), superior region, inferior region, temporal region and nasal region in the inner ring (SI, II, TI and NI), and superior region, inferior region, temporal region and nasal region in the external ring (SE, IE, TE and NE).

**Statistical analysis**

All statistical evaluation was done using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Data were expressed as the mean ± standard deviation (SD). Refraction data were converted to SEs, calculated as the spherical dioptric power plus one-half of the cylindrical dioptric power. One way analysis of variance (ANOVA) was used to test for the difference among the healthy controls and the NMOSD group with post hoc tests used between the pair. Pearson correlation coefficients were calculated.
to assess correlations between the intra-retinal layer thickness and microvascular density. P-values less than 0.05 (P < 0.05) were considered to be statistically significant.

Results

There was no significant difference in the age, gender, and IOP as shown in Table 1. The BCVA was significantly different between the two groups (P < 0.05) with the NMOSD patients showing a reduced BCVA. In NMOSD patients, 8 eyes (40%) had a 1-time history of ON attack and 6 eyes (30%) had a history of ON attack for 2 or more times.

Comparison of macular microvascular density from OCT-A

Figure 1 shows typical images of all vascular network maps of OCT-A in patients with NMOSD and healthy controls with their microvascular density value. Microvascular density in macula was significantly reduced in the total annular zone (TAZ), three concentric zones (C1-C3) around the fovea and the quadrantal zones (S, T, I and N) of the NMOSD patients in all three capillary plexuses when compared to the healthy controls (Figure 2). There was no significant difference in the microvascular density between the SRCP and DRCP in the eyes with NMOSD. However, in control eyes, the capillary plexus of the DRCP was denser than that of the SRCP (P < 0.05). Reduced microvascular density in the SRCP (r = 0.766, P < 0.001) and DRCP (r = 0.806, P < 0.001) had significant correlation with the frequency of ON attack.

Comparison of 3D thickness map of individual retinal layer

Compared to the control group, the total macular thickness was significantly thinner (P < 0.001, Figure 3) in all regions except in the central region. NMOSD patients showed thinner RNFL in the nasal, temporal and central region when compared to the healthy controls. All regions of the GCIPL was significantly reduced (P < 0.05, Figure 3) in NMOSD patients when compared to the healthy controls. NMOSD patients showed significantly thickened (P < 0.05, Figure 3) inner ring of the superior and inferior quadrant and external ring of the nasal quadrant of the INL when compared to the control group. The inferior quadrant of the HFL+ONL in NMOSD patient was significantly reduced (P < 0.001, Figure 3) when compared to the control group.

Correlation of macular microvascular density with individual retinal layer thickness and visual acuity

In NMOSD patients, there were significant correlation between the TAZ microvascular density in SRCP and the average RNFL thickness (r = 0.576, P = 0.006, Figure 4) and the average GCIPL thickness (r = 0.706, P < 0.001, Figure 4) respectively. Also, there were significant correlations between the TAZ
microvascular density in DRCP and the average RNFL thickness ($r = 0.761$, $P < 0.001$, Figure 4) and the
average GCIPL thickness ($r = 0.834$, $P < 0.001$, Figure 4) respectively.

For NMOSD group, VA moderately correlated with the TAZ microvascular density in SRCP ($r = 0.562$, $P$
$= 0.003$, Figure 5), and strongly correlated with TAZ microvascular density in DRCP ($r = 0.816$, $P <$
0.001, Figure 5) respectively.

Discussion

This study evaluated the changes of macular microvascular network in NMOSD eyes by using OCT
angiography for the first time. Using the quantitative measures of OCT-A, we have shown that
microvascular density of NMOSD was significantly lower than the values of healthy controls both in
superficial and deep vascular layers. Furthermore, the times of ON attack played an important role in the
reduction of macular microvascular density. We also found that decreased macular microvascular density
positively correlated with the thinning of retinal ganglion complex (RNFL and GCIP) and with the
worsening of the visual acuity in NMOSD patients.

There are several possible reasons for the decreased microvascular density around the macula in NMOSD
patients. Firstly, NMOSD\textsuperscript{12,24,25} and ON\textsuperscript{26,27} damages and reduces the number of nerve fiber and ganglion
cells in the macula, and in turn, reduces the metabolic activities. The reduced load in metabolic demand
lowers retinal perfusion via auto regulatory mechanisms. As evident in our current and previous studies,
NMOSD and ON are associated with inner retinal atrophy including RNFL and GCIP thinning using
structural OCT system, which are two structural markers of axonal and ganglion cell degeneration\textsuperscript{12,24}.

Secondly, there could be primary vascular dysfunctions, such as endothelial abnormalities that have been
noted in the brains of patients with NMOSD\textsuperscript{28,29}. In our current study, the average RNFL and GCIP
thinning may be causally related to the described macular microvascular changes. Similar to glaucoma
and non-arteritic anterior ischemic optic neuropathy, vascular mediated optic neuropathies are known to
cause injury to the nerve fibers and ganglion cells located in the inner retinal layers\textsuperscript{30}. Because both
vascular changes and extent of RNFL/GCIP thinning are associated with NMOSD and ON, the cross-
sectional nature of the current study cannot resolve whether the reported macular microvascular changes
precede or occur secondary to RNFL and GCL thinning. Undoubtedly, longitudinal studies are needed to
be done to evaluate this viewpoint.

No significant difference in the microvascular density was found between SRCP and DRCP in NMOSD
patients; in the HC group, the microvascular density of DRCP was denser than that of SRCP. This result
indicated that more capillaries in DRCP are lost in NMOSD patients with a history of ON. This
phenomenon may be attributed to the different anatomic structure of the deep and superficial capillary
plexus\textsuperscript{31}. The density of the capillaries in the deep plexus is greater than in the superficial layer, as evident in the HC group in the current study. Capillaries are responsible for the diffusion of oxygen in the body, thus since the DRCP contains more capillaries it may be the most perfused region of the retina. Therefore, any insult to it may reduce the retinal perfusion. This speculation needs to be verified in future studies.

Interestingly, we found thickening in some portions of the INL in NMOSD patients when compared to the healthy controls in this study. Our finding is consistent with previous studies that have reported of microcystic macular edema in the INL of NMOSD patients independent of optic nerve damage\textsuperscript{32,33}. We speculate that the selective thickening in some portions of the INL may be due to the dysfunction of the AQP4 in the Muller cells as previously reported\textsuperscript{33,34}. Also, the effect of the activation of retinal microglia located in the inner INL\textsuperscript{35}, as a response to the optic nerve injury \textsuperscript{32}, may play a role in the INL thickening.

Worth mentioning is the thinning of the HFL+ONL in NMOSD patients when compared to the healthy controls. Our finding is congruent with previous studies\textsuperscript{36} suggesting that inflammation of the Muller cells secondary to a direct attack by the AQP4 antibody may lead to the thinning of HFL+ONL in NMOSD\textsuperscript{37}. The significant thinning in the inferior quadrant may be the effect of gravity on the Muller cells, moving it into the inferior part of the HFL+ONL. Our present study did not find any significant changes in the ORL which is contrary to Cheng’s report\textsuperscript{10}, Cheng et al\textsuperscript{10} suggest that NMO patients had a thicker ORL than the controls because of the compensatory proliferation of these three layers as a protection against the axonal and neuronal degeneration. This discrepancy may be due to the different type of patients enrolled. In our study, eyes of NMOSD did not have ON when enrolled while Cheng et al\textsuperscript{10} enrolled patients who had ON.

Correlational analysis revealed that reduction of microvascular density at DRCP strongly correlated with worsening VA in NMOSD patients, suggesting that after ON attack, reduced retinal perfusion in response to the inflammatory or other pathologies may lead to photoreceptor damage. As a compensatory mechanism of the failed choroidal circulation, the deep capillary plexus of the inner retinal vasculature contributes more to the metabolic demands of the outer retina that it would normally\textsuperscript{38,39}. Furthermore, ischemia in the deep plexus contributes to the disruption of the photoreceptor layer\textsuperscript{40}, thus resulting in the decrease of visual acuity. We also found a moderate correlation between the decreased microvascular density at SRCP and visual acuity, suggesting that the superficial plexus vasculature may also contribute to the metabolic demands of the outer retina. Although we did not correlate the microvascular density with photoreceptor layer or other outer retinal layers directly in this study, the association between visual acuity and microvascular density suggests that microvascular network measurement in the inner retinal vascular layer may be useful in predicting visual acuity damage in NMOSD, particularly in eyes with a history of ON attack.
Studies using structural OCT have previously shown the retinal degeneration in NMOSD, particularly thinning of the peripapillary retinal nerve fiber layer\textsuperscript{3,4} and loss of ganglion cells\textsuperscript{10}. Nonetheless, few studies have reported on the retinal vascular abnormalities in NMOSD due to the limited technology\textsuperscript{11,12}. Fluorescein angiography is useful in demonstrating the retinal vasculature, but it cannot be performed frequently due to its invasive nature. OCT-A is a new advanced imaging technology that enables the non-invasive imaging of the retinal capillaries and is especially useful for in-depth analysis of retinal vessels in multiple layers that were previously visible on histopathological examination. Our data nonetheless suggest that OCT-A measurement of the retinal microvascular network with quantitative analysis may be a potential adjunct to detect vascular changes in NMOSD and provide a new imaging target for the management of NMOSD.

Concerning limitations of this study, the participants were limited to the Chinese population thus it is unclear whether these findings can be generalized across other ethnicities. Lack of pathological examination of eyes with NMOSD is the second. We were not able to conclude that anti-AQP4 antibodies were directly attacking the eyes with NMOSD, thus histopathological examinations would enable the confirmation of our hypothesis. Another limitation is that the cross-sectional nature of the study limits our ability to draw a definite conclusion in assessing the temporal patterns and long-term implications of the changes in the retinal microvasculature on the incidence and progression for NMOSD. Despite the presence of the algorithm to reduce motion artifacts, some of the OCT-A images still had motion artifacts owing to patients’ eye movement. We also observed a few projection artifacts, a well-described limitation at the deep plexus of the OCT-A images and were excluded from our analysis. With the technology still in its infancy, further enhancement of the software is needed to improve its reproducibility and usability for other diseases in the future.

In summary, we showed the significant retinal microvascular abnormality in NMOSD patients. We also demonstrated that micro structural damaged in the individual retinal layer in NMOSD patients. The reduction in microvascular densities were positively correlated with neuroaxonal structural damage, including RNFL and GCIPL thinning. Moreover, the reductions in the microvascular densities had significant correlations with the worsening of visual acuity. Our findings suggest that quantitative measurement of macular microvascular using OCT-A may be useful in evaluating the macular involvement and predicting the degree of VA damage with the progression of NMOSD disease.
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b. Financial Disclosures:

The authors have no proprietary interest in any materials or methods described in this article.

c. Other Acknowledgments:

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References


Figure Legends

Figure 1. Representative OCT-A images in the superficial, deep and whole retinal capillary plexus of an eye with NMOSD and a healthy control eye. The images were acquired in 3x3 mm areas around the fovea. The left column represents the OCTA SRCP image of NMOSD patient (Top), healthy control (Middle) and the segmentation of the SRCP (Bottom). The middle column represents the OCTA DRCP image of NMOSD patient (Top), healthy control (Middle) and segmentation of the DRCP (Bottom). The right column represents the OCTA WRCP of NMOSD patient (Top), healthy control (Middle) and segmentation of WRCP (Bottom). SRCP: superficial retinal capillary plexus superficial retinal capillary plexus; DRCP: deep retinal capillary plexus; WRCP: whole retinal capillary plexus.

Figure 2. Comparison of the microvascular density between patients with NMOSD and healthy controls. (Top) Comparison in SRCP. A significant reduction was seen in the superficial retinal capillary plexus in NMOSD patients when compared to the healthy controls. (Middle) Comparison in DRCP. A significant reduction was seen in the DRCP in NMOSD patients when compared to the healthy controls. (Bottom) Comparison in WRCP. A significant reduction was seen in most of the zones in NMOSD patients when compared to the healthy controls. * P<0.05.

Figure 3. Comparison of the retinal thickness between patients with NMOSD and healthy controls. (Top row) the intra-retinal layer thickness and total macular thickness maps of healthy controls. (Middle row) the intra-retinal layer thickness and total macular thickness maps of NMOSD patients. The thickness value is indicated by the colors shown in the color bar for each row. (Bottom row) the difference of the corresponding retinal layer thickness between the healthy controls and the NMOSD patients; blue represents significant thinning (P < 0.05), red represents significant thickening (P < 0.05). RNFL: retinal nerve fiber layer; GCIP: ganglion cell layer and inner plexiform layer; INL: inner nuclear layer; OPL: outer plexiform layer; HFL+ONL: Henle fiber layer and outer nuclear layer; ORL: outer retinal layer, which consists of the inner segment and outer segment of the photoreceptors and the retinal pigment epithelium and the total macular layer.

Figure 4. Correlation of microvascular density and average intra-retinal thickness in NMOSD patients. Correlation of the average RNFL thickness and microvascular density in the TAZ of SRCP. (Top left) Correlation of the average RNFL and microvascular density in the TAZ of DRCP. (Top right) Correlation of the average GCIP thickness and microvascular density in the TAZ of SRCP. (Bottom left) Correlation of the average GCIP thickness and microvascular density in the TAZ of DRCP (Bottom right). TAZ: total annular zone; SRCP: superficial retinal capillary plexus; DRCP: deep retinal capillary plexus.

Figure 5. Correlation between the microvascular density and visual acuity. (Left) Correlation between visual acuity and microvascular density in the TAZ of SRCP. (Right) Correlation between visual acuity and microvascular density in the TAZ of DRCP. TAZ: total annular zone; SRCP: superficial retinal capillary plexus; DRCP: deep retinal capillary plexus.
Table 1. Demographics of patients with NMOSD and normal subjects.

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<td>≥2 times</td>
<td>30% (6/20)</td>
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Values are mean ± standard deviation.
NMOSD: Neuromyelitis optica spectrum disease group.
BCVA: Best corrected visual acuity. AL: Axial length (measured in millimeters, mm). IOP: Intra-ocular pressure (measured in millimeter of mercury, mmHg). ON: optic neuritis.
* P <0.05
Table 2. Comparison of microvascular density between the superficial and deep retinal capillary plexus in the healthy controls and NMOSD patients.

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<td>SD</td>
<td>0.0476</td>
<td>0.0613</td>
<td>0.0484</td>
<td>0.0452</td>
<td>0.0468</td>
<td>0.0475</td>
<td>0.0629</td>
<td>0.0508</td>
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<tr>
<td>DRCP</td>
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<tr>
<td>Mean</td>
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<td>0.6474</td>
<td>0.6331</td>
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<td>0.0885</td>
<td>0.0607</td>
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<tr>
<td>P value</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tr>
</tbody>
</table>

Two scatter plots are shown, each depicting the relationship between visual acuity and the density of different structures.

1. **TAZ SRCP density (%) vs. Visual Acuity**
   - Correlation coefficient: \( r = 0.562 \)
   - P-value: \( P = 0.003 \)

2. **TAZ DRCP density (%) vs. Visual Acuity**
   - Correlation coefficient: \( r = 0.816 \)
   - P-value: \( P < 0.001 \)
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