An Optical Coherence Tomography Study that Supports the Neurovascular Basis of Schizophrenia Disease

ABSTRACT

Objectives: Spectral domain optical coherence tomography (SD-OCT) is a non-penetrating, quick, and practical device which enables measurement of the chorioretinal layers. In this study, our purpose was to investigate the retinal nerve fiber layer (RNFL) and choroidal thickness in schizophrenia patients, using SD-OCT, and compare the findings with those of the control group.

Methods: For the study, 44 patients with a diagnosis of schizophrenia, and 41 age- and gender-matched healthy controls were enrolled. Both eyes of each participant were evaluated. RNFL was measured and analyzed automatically with optical coherence tomography. Scans for choroidal thickness were obtained with the enhanced depth imaging mode of the SD-OCT device and measured manually.

Results: The average age of schizophrenia patients was 47.82, and it was 45.5 for the control group. The mean illness duration of the patients was 24.79 years. According to the results of this study, all choroidal measures (nasal, subfoveal, and temporal) of both eyes, and the RNFL thickness of schizophrenia patients, were significantly thinner than that of healthy controls. The chorioretinal measures of both eyes were similar. The results showed that a weak negative correlation was present between illness duration and choroidal diameter.

Conclusion: In addition to demonstrating the thinning of RNFL in schizophrenia patients, as frequently reported in the literature, the results of this study show, for the first time, that choroidal thickness is considerably decreased in schizophrenia patients compared to the healthy controls, using SD-OCT. Keeping in mind that the choroid is a vascular layer, these results support the neurovascular hypothesis of schizophrenia.

Keywords: Clinical trials, psychiatric disorders, psychopathology, schizophrenia

Introduction

Schizophrenia is a chronic, ingravescent, usually devastating disease, with positive, negative, affective, and cognitive symptoms.1 Although its etiopathogenesis is not completely understood, one of the proposed models is the neurodegeneration model.2

The brain and retina have many structural and functional similarities, such as both being derived from the neuroectoderm and having similar neural cells and layered structures. They are also connected with the optic nerve.3 The retina is visible and can be examined using special instruments, and the pathologic changes occurring in the brain in several neurodegenerative diseases can also be seen in the retina.4-6 Optical coherence tomography (OCT) has emerged as a non-penetrating, rapid, and easy-to-use method of retinal imaging which enables practitioners to examine the retina and its layers in high resolution. Although it is mainly used to study several degenerative ophthalmic diseases, many studies also show a decrease in retinal nerve fiber layer (RNFL) diameter in some neurodegenerative illnesses of the brain, like mild cognitive disturbance, Alzheimer’s dementia (AD), Parkinson’s disease (PD), multiple sclerosis (MS), and Huntington’s disease (HD).4-8

Aydın Kurt1, Kürşad Ramazan Zor2, Erkut Küçük2, Gamze Yıldırım2, Etem Erdal Erşan3

1Department of Psychiatry, Niğde Omer Halisdemir Training and Research Hospital, Niğde, Turkey
2Department of Ophthalmology, Niğde Omer Halisdemir Training and Research Hospital, Niğde, Turkey
3Department of Psychiatry, Niğde Omer Halisdemir University School of Medicine, Niğde, Turkey

This study was presented at the Interactive Psychiatry Education Congress and received the 3rd prize. (IPEK, October 10-13, 2019; Antalya, Turkey).

Corresponding author: Aydin Kurt  aydinkurt20@yahoo.com

Received: February 18, 2021
Accepted: July 10, 2021

Cite this article as: Kurt A, Ramazan Zor K, Küçük E, Yıldırım G, Erdal Erşan E. An optical coherence tomography study that supports the neurovascular basis of schizophrenia disease. Alpha Psychiatry. 2022;23(1):12-17.

Copyright©Author(s) - Available online at alpha-psychiatry.com. Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
In the last decade, based on the consistent results related to neurodegenerative diseases and the neurodegenerative hypothesis on the etiology of schizophrenia, several studies have used OCT to evaluate the retinal layers and structures in schizophrenia patients. While many studies using OCT revealed that the RNFL in schizophrenia patients was considerably thinner than that of the control groups, others reported no difference in RNFL thickness between the patient and control groups.

Another hypothesis for schizophrenia pathogenesis is the microvascular changes in the brain vasculature. In a postmortem study of schizophrenia patients, Uranova et al. found severe structural distortions and changes in the prefrontal and visual cortex capillaries. Long-term mild inflammation that has been related to increased vascular risk is reported in schizophrenia patients. The choroid is composed of a vascular network, and its thickness can change in response to autonomic nervous system input and inflammation.

The data about the structure and layers of the retina obtained from OCT support the data about functional changes in the retina obtained from electroretinography (ERG). A considerable association between the decrease in RNFL thickness in OCT and the low amplitude and late latency in ERG have been reported by some researches. A few studies in schizophrenia patients have reported a decrease in RNFL thickness and a delayed latency in ERG, but the direct relationship between OCT and ERG has not been shown.

We hypothesize that the choroidal layers of the schizophrenia patients may be affected by the neurovascular and neurodegenerative processes. To date, 2 studies have evaluated choroidal layers using OCT and both have reported conflicting results. While there are many studies about RNFL thickness in schizophrenia patients, there is little research about the choroid layer in these patients. We hypothesize that the choroidal thickness and RNFL of schizophrenia patients are thinner than those of healthy individuals. The purpose of this research was to demonstrate in particular the difference between the choroidal thickness values of schizophrenia patients and healthy controls, using spectral domain optical coherence tomography (SD-OCT).

**Methods**

The study was conducted with patients diagnosed with schizophrenia or schizoaffective disorder, between the ages of 18 and 64, who were followed and treated between June 15, 2019, and December 15, 2019, in the outpatient or inpatient psychiatry clinics of Niğde Training and Research Hospital. An age- and sex-matched (P = 1.000) control group was formed of healthy individuals who accepted to participate in the study.

Exclusion criteria: (1) Patients who had mental retardation or comorbid psychiatric disorders, (2) Patients who had neurodegenerative diseases, such as AD, PD, or MS, (3) Patients with a history of uveitis, glaucoma, or invasive retinal interventions, (4) Patients who had diabetic retinopathy or hypertensive retinopathy on retinal examination, (5) Patients with a spherical refractive error greater than ± 3.0 D and/or cylindrical error greater than ± 2.0 D, (6) Patients with intraocular pressure greater than 21 mmHg in the ophthalmic examination, and (7) Patients with low-quality OCT scans (signal strength ≤ 6) were excluded from the study. Additionally, participants with psychiatric diseases were excluded from the control group.

The ethical confirmation of the study was received from the Ethics Committee of Niğde Ömer Halisdemir University (February 27, 2019/02-13). All researchers accepted to conduct the study according to the tenets of the Declaration of Helsinki. Detailed information about the study process was provided to all participants, and an informed consent form was signed by all participants and their legal guardians.

The diagnosis of schizophrenia was made using a semi-structured interview based on DSM-5 criteria. Autorefractometry was performed for all participants, Goldmann applanation tonometry was used to measure intraocular pressure, and biomicroscopy and fundus examinations were performed. The sociodemographic, clinical, and ophthalmological data of the patients were recorded using the form prepared by the researchers. The Positive and Negative Syndrome Scale (PANSS) scale was used to survey the intensity of clinical symptoms in schizophrenia patients. Validity and reliability studies of the Turkish version of this scale were conducted. The retinal layers of both groups were measured using the Cirrus HD-OCT device (Carl Zeiss Meditec Inc., Dublin, CA, USA).

The RNFL thickness was measured automatically by the device, while the choroidal layer thickness was measured manually. In this study, the images were obtained by following the HD 5 Line Raster protocol, consisting of 6 mm parallel lines with 1024 A-scan/B-scan and 0.25 mm spacing, which was reduced to single line. The choroidal layer was visualized in SD-OCT in the enhanced depth imaging (EDI) mode. The first measurement was made under the fovea. Then, keeping the first measurement point constant with the help of the device ruler function, 3 temporal and 3 nasal measurements were obtained in the same way from a total of 6 points in the temporal and nasal aspects, with 500 μm gaps up to 1500 μm on the hyperrereflective RPE band. The mean values for nasal and temporal choroidal thickness were obtained by adding 500-, 1000-, and 1500-μm measurement values and dividing them by the total number of measurements. Three nasal-temporal-subfoveal choroidal thickness values were used for comparison. Two ophthalmologists blinded to the groups measured the choroidal thickness separately. To prevent diurnal variations in choroidal thickness, OCT scans were obtained between 11 AM and 12 PM, within one hour, everyday by the same experienced technician.

**Statistical Analysis**

SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical evaluation of the data obtained in our study. The skewness and kurtosis values and histogram graph of dependent variables were checked for patient and control groups while examining normality.

**MAIN POINTS**

- For the first time, results of this study shows that choroidal thickness is significantly decreased in schizophrenia patients compared to the healthy controls using SD-OCT.
- Because of the intense vascular nature of choroid layer, choroidal thinning in schizophrenia patients support the neurovascular hypothesis of schizophrenia.
- There was a weak negative correlation between illness duration and choroidal thickness.
The average age of the schizophrenia patients and healthy controls was 47.82 and 45.59, respectively, and the groups were similar in terms of age ($P = .270$) and sex ($P = 1.000$). Thirty-seven patients (84.1%) were diagnosed with schizophrenia. The average illness duration of the patients was 24.79 years. The measures of intraocular pressure and the contribution of the systemic disease ($P = .904$) between the patient and the control groups were similar. Thirty-four (77.3%) of the patients were from the outpatient clinic, and were in remission or partial remission; only 10 (22.7%) were inpatients and had new psychotic exacerbations. The detailed sociodemographic and clinical data of the groups are represented in Tables 1 and 2.

According to the results of this study, all choroidal measures (nasal, subfoveal, and temporal) of both eyes and the RNFL measures were statistically significantly lower in the schizophrenia patients than in the healthy controls. The comparison of the choroidal measurements between the groups is given in Table 3.

A paired-samples $t$-test was performed to evaluate the intereye variability of the data obtained from both eyes. According to statistical evaluation, there was no difference in the chorioretinal measurements between both the eyes. Detailed results are shown in Table 4.

Pearson correlation coefficient was obtained to examine the relationships between variables, and the detailed data are shown in Table 5. The PANSS evaluates the symptom severity of the disease. According to this study, there was a slight inverse relationship between the duration of illness and the measurements of the left nasal and left subfoveal choroidal thickness, but no correlation was found between the other retinal diameter measurements. While there was a slight positive relationship between PANSS total scores and choroidal thickness, the PANSS positive scores were independent of all measurements. Finally, a weak positive relationship was demonstrated between RNFL diameter and PANSS negative scores.

### Discussion

The first parameter evaluated in this study was the RNFL thickness. We determined that the patients diagnosed with schizophrenia had significantly thinner RNFL than the control group. RNFL thinning in schizophrenia patients has been shown in many studies in the literature to-date, and there is almost a consensus on this issue.2,5,11,13,15,17,28 Only 2 studies have reported similar RNFL measures between the groups.16,17 The Stratus OCT device, with lower resolution than the current devices, was used in the study by Chu et al,16 which reported that there was no diversity in terms of RNFL thickness between the patient and control groups. The study by Topçu-Yılmaz et al17 included patients with an acute attack, and reported that the inflammatory process which may be seen in patients with acute attack may mask the thinning in the retinal nerve. In order to perform RNFL measurements with the OCT device in the follow-up of schizophrenia patients, it seems necessary to reveal whether RNFL is related to the illness duration and the intensity of the symptoms. Yılmaz et al13 and Ascaso et al14 could not find a correlation between RNFL thinning and illness duration in their studies. Schönfeldt-Lecuano et al18 and Lee et al19 found a negative correlation between the illness duration and RNFL in their studies. Similar to Yılmaz et al13, a relationship between illness duration and RNFL thickness was not determined in this study. Lee et al19 could not detect a relationship between PANSS scores and RNFL. Thus, they reported that no relationship could be observed between disease symptoms and RNFL. Celik et al20 detected a weak

### Table 1. Demographic and Clinical Data of the Patient and Control Groups

| Group                  | Patient | Control | $P$  |
|------------------------|---------|---------|------|
| Age, mean (SD)         | 47.82 (9.44) | 45.59 (9.92) | .270 |
| Gender                 |         |         | 1.000|
| Female                 | 14 (31.8) | 13 (31.7) |     |
| Male                   | 30 (68.2) | 28 (68.3) |     |
| Systemic disease       |         |         | .904 |
| Yes                    | 9 (20.5) | 7 (17.1) |     |
| No                     | 35 (79.5)| 34 (82.9)|     |
| Intraocular Pressure, mean (SD) | 16.02 (4.26) | 15.02 (2.57) | .190 |
| Right                  |         |         |      |
| Left                   | 16.06 (3.64) | 15.21 (2.45) | .210 |

### Table 2. Clinical Data and Scale Scores of Patient Group

| Diagnosis                  | n (%)  |
|----------------------------|--------|
| Schizophrenia              | 37 (84.1) |
| Schizoaffective disorder   | 7 (15.9)  |
| Drugs                      |         |
| AAP                        | 32 (72.7) |
| AAP+MS                     | 12 (27.3) |
| mean (SD)                  |         |
| Disease duration           | 24.79 (15.22) |
| PANSS total                | 102.30 (16.56) |
| PANSS positive             | 23.32 (5.79) |
| PANSS negative             | 27.23 (6.84) |
| PANSS general              | 51.95 (8.26) |

AAP, atypical antipsychotics; MS, mood stabilizers; PANSS, Positive and Negative Syndrome Scale.
inverse relationship between PANSS scores and RNFL, but there was a stronger correlation between the ganglion cell layer and the internal plexiform layer values and PANSS scores. In our study, as in the research of Lee et al, we did not determine a statistically considerable relationship between RNFL and PANSS scores, but unlike the other studies, there was a poor positive correlation between RNFL and PANSS negative scores.

In recent studies, it has been emphasized that the neovascular unit could potentially contribute to the pathophysiology of schizophrenia.21,29,30 Neuroimaging studies reporting that the neurovascular unit is involved in schizophrenia have shown local or widespread hypoperfusion areas in the brain.31-33 Burghardt et al reported diffuse vascular endothelial cell disorder in patients with schizophrenia. In the same study, they stated that endothelium-derived nitric oxide, which increases blood flow by causing vasodilation, was decreased in schizophrenia patients. The negative effects of neuroinflammation on neurovascular unit function in patients with schizophrenia have been shown in many studies.21

In our study, in all choroidal thickness measurements (subfoveal, nasal, and temporal choroid layer thickness of both eyes), statistically significant thinning was detected in the schizophrenia patients compared to the healthy controls. Our study shows that the neurovascular unit is affected in patients with schizophrenia, which supports

| Table 3. Comparison of Retinal Nerve Fiber Thickness and Nasal, Temporal, and Subfoveal Choroidal Thickness in Patient and Control Groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Variable**    | **Group**       | **n**           | **Mean (SD)**   | **P**           |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Right nasal choroidal thickness (μm) | Patient | 44 | 233.02 (41.59) | .004 |
|                 | Control         | 41 | 262.87 (49.99) | .004 |
| Right subfoveal choroidal thickness (μm) | Patient | 44 | 266.70 (40.59) | <.001 |
|                 | Control         | 41 | 300.78 (44.78) | <.001 |
| Right temporal choroidal thickness (μm) | Patient | 44 | 229.75 (47.61) | <.001 |
|                 | Control         | 41 | 271.19 (47.88) | .039 |
| Left nasal choroidal thickness (μm) | Patient | 44 | 243.54 (49.45) | .039 |
|                 | Control         | 41 | 269.39 (63.95) | .039 |
| Left subfoveal choroidal thickness (μm) | Patient | 44 | 267.93 (48.02) | .001 |
|                 | Control         | 41 | 304.75 (54.21) | .001 |
| Left temporal choroidal thickness (μm) | Patient | 44 | 237.11 (45.84) | <.001 |
|                 | Control         | 41 | 279.95 (50.67) | <.001 |
| Right RNFL      | Patient         | 44 | 87.04 (9.64)   | .017 |
|                 | Control         | 41 | 91.78 (8.13)   | .017 |
| Left RNFL       | Patient         | 44 | 85.13 (7.20)   | .003 |
|                 | Control         | 41 | 90.58 (8.90)   | .003 |

nP < .05.
RNFL, retinal nerve fiber layer.

| Table 4. Comparison of Retinal Nerve Fiber Thickness and Nasal, Temporal, Subfoveal Choroidal Thickness Right and Left Eye |
|-------------------------------------------------------------------------------------------------------------------|
| **Variable** | **Group** | **n** | **Mean (SD)** | **P** |
|---------------|-----------|-------|---------------|-------|
| Nasal choroidal thickness (μm)                              | Right     | 85    | 247.42 (47.97)| .079  |
|               | Left      | 85    | 256.01 (58.08)| .079  |
| Subfoveal choroidal thickness (μm)                          | Right     | 85    | 283.14 (45.74)| .511  |
|               | Left      | 85    | 285.69 (54.07)| .511  |
| Temporal choroidal thickness (μm)                           | Right     | 85    | 249.74 (51.83)| .100  |
|               | Left      | 85    | 257.78 (52.56)| .100  |
| RNFL           | Right     | 85    | 89.33 (9.21)  | .087  |
|               | Left      | 85    | 88.76 (8.47)  | .087  |

nP < .05.
RNFL, retinal nerve fiber layer.

| Table 5. Investigation of Relationship of Retinal Nerve Fiber Layer and Choroidal Thickness with Disease Duration and PANSS Values in Patients |
|-------------------------------------------------------------------------------------------------------------------|
| **Pearson correlation analysis**                                                                                       |
| **Disease Duration** | **PANSS** | **PANSSp** | **PANSSn** | **PANSSg** |
|----------------------|-----------|------------|------------|------------|
| **Variable**         | **r**     | **P**      | **r**      | **P**      |
| Right nct            | −0.17     | .271       | 0.34       | .025*      |
| Right sct            | −0.29     | .060       | 0.35       | .019*      |
| Right tct            | −0.04     | .792       | 0.27       | .073       |
| Left nct             | −0.37     | .010       | 0.38       | .011*      |
| Left sct             | −0.37     | .010       | 0.48       | .001*      |
| Left tct             | −0.28     | .62        | 0.48       | .001*      |
| Right RNFL           | −0.02     | .894       | 0.26       | .092       |
| Left RNFL            | −0.07     | .634       | 0.22       | .129       |

*r < .05; P < .01.
**nct, nasal choroidal thickness; sct, subfoveal choroidal thickness; tct, temporal choroidal thickness; RNFL, retinal nerve fiber layer; PANSS, Positive and Negative Syndrome Scale; r, Pearson correlation coefficient.
many previous studies. According to the literature review, this is the first research study to show that the choroidal layer is significantly thinner in schizophrenia patients than in healthy controls. In a previous study which reported a similar result, the choroidal thickness of 6 schizophrenia and bipolar disorder patients with psychotic symptoms were compared with the data of 18 healthy individuals matched for age and sex. In their study, a statistically insignificant thinning in the choroidal layer was detected in patients with psychotic symptoms. However, the lack of time points at which the OCT examinations were performed in their study seems to be an important methodological problem because the thickness of the choroid layer is affected by diurnal variations. Tan et al reported that the thickness of the choroidal layer changes during the day. It is generally the thickest in the early hours, and diminishes later in the day. The low number of patients and the lack of detailed eye examination data are other issues that decrease the reliability of this result. In contrast to our study, Topcu-Yilmaz et al, found no difference in the choroidal thickness between groups, in their study. They compared the choroidal diameter of 59 schizophrenia patients with acute exacerbation who were followed in the inpatient psychiatry clinic, with a control group of 36 healthy individuals matched for age and sex, while in our study, a significant proportion of the patients (34 patients, 77.3%) were in remission or partial remission and were followed up as outpatients. In a study by Ascaso et al, the retinal layers of schizophrenia patients with acute exacerbation and of patients in remission or partial remission were compared with those of healthy controls using OCT, and there was no significant disparity in RNFL thickness measurements between the patients with acute exacerbation and those in the control group, while RNFL diameter was considerably diminished in patients in remission. The researchers attributed this to the ongoing inflammatory process in patients with acute exacerbation and claimed that inflammation led to the thickening of the retinal layers, which masks the thinning. Since Topcu-Yilmaz et al conducted their study in patients with an acute attack of schizophrenia, the ongoing inflammatory processes may be responsible for the absence of disparity between the groups in terms of choroidal layer thickness.

We detected a weak inverse relationship between illness duration and choroidal diameter in this study. A similar correlation was shown in the study by Topcu-Yilmaz et al, but no relationship was detected between the illness duration and choroidal diameter in the study by Joe et al. Moreover, a positive relationship was detected between the PANSS total and negative scores and the choroidal thickness in our study. The correlation was thought to be related to the PANSS positive scores, because there was no relationship between PANSS positive scores and the choroidal diameter.

The results of our study, together with the other studies using OCT in schizophrenia patients, give rise to hope that OCT can be used in the diagnosis and screening of neurodegenerative diseases such as schizophrenia, due to the scarcity of studies on choroidal thickness, especially on RNFL thickness. However, the lack of correlation between the severity and duration of the illness and the OCT findings reduces the possibility of using the OCT device for disease staging.

The use of atypical antipsychotic drugs by all patients in the study is a limitation of this research. However, the active ingredients of these drugs were different, and the profiles of the metabolic side effects of each drug differed. Therefore, it is not possible to exclude the effects of atypical antipsychotic drugs on retinal layers and vessels.

In our study, the RNFL thinning and the reduction in choroidal thickness in schizophrenia patients, determined by the SD-OCT device, support the claim that the neurovascular unit is affected in schizophrenia. If the role of neurovascular abnormalities in the neurobiology of schizophrenia can be fully explained, therapies to target these abnormalities may be promising.

In conclusion, while it has been repeatedly shown that RNFL thickness, measured by SD-OCT which is an easy-to-use, fast, and non-invasive imaging method, decreases in both neurological diseases and in psychiatric diseases like schizophrenia, this study has, for the first time, shown that choroidal thickness decreases significantly in schizophrenia patients. SD-OCT appears to be a beneficial method for the diagnosis and follow-up of schizophrenia. The investigation of chorioretinal abnormalities in schizophrenia patients with further well-planned future studies in this area may increase the value of this method.

Ethics Committee Approval: Ethics committee approval was received for this study from the Niğde Ömer Halisdemir University (Approval Date: February 27, 2019; Approval Number: 02-13).

Informed Consent: Written informed consent was obtained from the participants and their legal guardians for the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept - A.K., K.R.Z., E.K., G.Y., E.E.E.; Design - A.K., K.R.Z., E.K., G.Y., E.E.E.; Supervision - A.K., K.R.Z., E.E.E.; Resources - A.K., K.R.Z., E.K., G.Y., E.E.E.; Materials - A.K., K.R.Z., E.K., G.Y., E.E.E.; Data Collection and/or Processing - A.K., G.Y.; Analysis and/or Interpretation - A.K., K.R.Z., E.K., G.Y., E.E.E.; Literature Review - A.K., K.R.Z., G.Y.; Writing - A.K., K.R.Z., E.K., G.Y.; Critical Review - A.K., K.R.Z., E.K., G.Y., E.E.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet. 2016;388(10039):86-97. [CrossRef]
2. Siever LJ, Davis KL. The pathophysiology of schizophrenia disorders: perspectives from the spectrum. Am J Psychiatry. 2004;161(3):398-413. [CrossRef]
3. London A, Benhär I, Schwartz M. The retina as a window to the brain-from eye research to CNS disorders. Nat Rev Neurol. 2013;9(1):44-53. [CrossRef]
4. Gao L, Liu Y, Li X, Bai Q, Liu P. Abnormal retinal nerve fiber layer thickness and macula lutea in patients with mild cognitive impairment and Alzheimer’s disease. Arch Gerontol Geriatr. 2015;60(1):162-167. [CrossRef]
5. Obis J, Cipres Alastuey M, Villades E, Garcia-Martin E, Satue M, Rodrigo MJ. Analysis of the peripapillary retinal nerve fiber layer and choroidal thickness in patients with Parkinson’s disease using swept-source optical coherence tomography. Acta Ophthalmol. 2016;94. [CrossRef]
6. Gatto E, Parisi V, Persi G, et al. Optical coherence tomography (OCT) study in Argentinean Huntington’s disease patients. Int J Neurosci. 2018;128(12):1157-1162 [CrossRef]
7. Paquet C, Boissonnot M, Roger F, Dighiero P, Gil R, Hugon J. Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer’s disease. Neurosci Lett. 2007;420(2):97-99. [CrossRef]

8. Siger M, Dziegielewski K, Jasek L, et al. Optical coherence tomography in multiple sclerosis: thickness of the retinal nerve fiber layer as a potential measure of axonal loss and brain atrophy. J Neurol. 2008;255(10):1555-1560. [CrossRef]

9. Ascaso FJ, Cabezon L, Quintanilla MA, et al. Retinal nerve fiber layer thickness measured by optical coherence tomography in patients with schizophrenia: a short report. Eur J Psychiat. 2010;24:227-235.

10. Cabezon L, Ascaso F, Ramiro P, et al. Optical coherence tomography: a window into the brain of schizophrenic patients. Acta Ophthalmol. 2012;90:249.

11. Lee WW, Tajunisah I, Sharmilla K, Peyman M, Subrayan V. Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: evidence from optical coherence tomography. Invest Ophthalmol Vis Sci. 2013;54(12):7785-7792. [CrossRef]

12. Ascaso FJ, Rodriguez-Jimenez R, Cabezon L, et al. Retinal nerve fiber layer and macular thickness in patients with schizophrenia: influence of recent illness episodes. Psychiatry Res. 2015;229(1-2):230-236. [CrossRef]

13. Yilmaz U, Kucuk E, Ulgan A, et al. Retinal nerve fiber layer and macular thickness measurement in patients with schizophrenia. Eur J Ophthalmol. 2016;26(4):375-378. [CrossRef]

14. Celik M, Kalenderoglu A, Sevgi Karadag A, Bekir Egilmez O, Han-Almis B, Simpek A. Decreases in ganglion cell layer and inner plexiform layer volumes correlate better with disease severity in schizophrenia patients than retinal nerve fiber layer thickness: findings from spectral optic coherence tomography. Eur Psychiat. 2016;32:9-15. [CrossRef]

15. Joe P, Ahmad M, Riley G, Weissman J, Smith RT, Malaspina D. A pilot study assessing retinal pathology in psychosis using optical coherence tomography: choroidal and macular thickness. Psychiatry Res. 2018;263:158-161. [CrossRef]

16. Chu EM, Kolappan M, Barnes TR, Joyce EM, Ron MA. A window into the brain: an in vivo study of the retina in schizophrenia using optical coherence tomography. Psychiatry Res. 2012;203(1):89-94. [CrossRef]

17. Topcu-Yilmaz P, Aydin M, Cetin Ilhan B. Evaluation of retinal nerve fiber layer, macular, and choroidal thickness in schizophrenia: spectral optic coherence tomography findings. Psychiatry Clin Psychopharmacol. 2019;29:1.

18. Andreasen NC, Calarge CA, O’Leary DS. Theory of mind and schizophrenia: a positron emission tomography study of medication-free patients. Schizophren Bull. 2008;34(4):708-719. [CrossRef]

19. Uranova NA, Zimin IS, Vikhreva OV, Krukov NO, Rachmanova VI, Orlovskaya DD. Ultrastructural damage of capillaries in the neocortex in schizophrenia. World J Biol Psychiat. 2010;11(3):567-578. [CrossRef]

20. Nguyen TT, Dev SI, Chen G, et al. Abnormal levels of vascular endothelial biomarkers in schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2018;268(8):849-860. [CrossRef]

21. Najjar S, Pahlajani S, De Sanctis V, Stern JNH, Najjar A, Chong D. Neurovascular unit dysfunction and blood-brain barrier hyperpermeability contribute to schizophrenia neurobiology: a theoretical integration of clinical and experimental evidence. Front Psychiatry. 2017;8:83. [CrossRef]

22. Sander BP, Collins MJ, Read SA. The effect of topical adrenergic and anticholinergic agents on the choroidal thickness of young healthy adults. Exp Eye Res. 2014;128:181-189. [CrossRef]

23. Sirem P, Wang C, Yianikas C, et al. Relationship between optical coherence tomography and electrophysiology of visual pathway in non-optic neuritis eyes of multiple sclerosis patients. PLoS One. 2014;9(8).

24. Adams SA, Nasrallah HA. Multiple retinal anomalies in schizophrenia. Schizophr Res. 2018;195:3-12. [CrossRef]

25. Yahia VN. Diagnostic and statistical manual of mental disorders S: a quick glance. Indian J Psychiatry. 2013;55(3):220-223. [CrossRef]

26. Kostakoglu AE, Batur S, Tiryaki A. Positive and Negative Syndrome Scale (PANSS) the validity and reliability of the Turkish version. Turk J Psychiat. 1999;14:23-32.

27. Silverstein SM, Fadakki SI, Demmin DL. Schizophrenia and the retina: towards a 2020 perspective. Schizophr Res. 2020;219:84-94. [CrossRef]

28. Schonfeld-Lecuona C, Kregel T, Schmidt A, et al. Retinal single-layer analysis with optical coherence tomography (OCT) in schizophrenia spectrum disorder. Schizophr Res. 2020;219:5-12. [CrossRef]

29. Katsel P, Roussos P, Plietnikov M, Haroutunian V. Microvascular anomaly conditions in psychiatric disease. Schizophrenia - angiogenesis connection. Neurosci Biobehav Rev. 2017;77:327-339. [CrossRef]

30. Moises HW, Wolfschläger D, Binder H. Functional genomics indicate that schizophrenia may be an adult vascular-ischemic disorder. Transl Psychiatry. 2015;5:e616. [CrossRef]

31. Schmidt-Kastner R, van Os J, Esquivel G, Steinhbusch HW, Rutten BP. An environmental analysis of genes associated with schizophrenia: hypoxia and vascular factors as interacting elements in the neurodevelopmental model. Mol Psychiatry. 2012;17(12):1194-1205. [CrossRef]

32. Erkow R, Sabri O, Steinmeyer EM, Bull U, Sass H. Psychopathological and SPECT findings in never-treated schizophrenia. Acta Psychiatr Scand. 1997;96(1):51-57. [CrossRef]

33. Schultz SK, O’Leary DS, Boles Ponto LL, et al. Age and regional cerebral blood flow in schizophrenia: age effects in anterior cingulate, frontal, and parietal cortex. J Neuropsychiatry Clin Neurosci. 2002;14(1):19-24. [CrossRef]

34. Burghardt K, Grove T, Ellingrod V. Endothelial nitric oxide synthetase genetic variants, metabolic syndrome and endothelial function in schizophrenia. J Psychopharmacol. 2014;28(4):349-356. [CrossRef]

35. Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in patients with mild cognitive impairment and Alzheimer’s disease. Invest Ophthalmol Vis Sci. 2012;53(1):261-266. [CrossRef]