DOI: 10.14744/DAJPNS.2024.00259
Dusunen Adam J Psychiatr Neurol Sci
2024;37:179-188

RESEARCH ARTICLE

# Retinal abnormalities and their relationship with social cognition in patients with schizophrenia and their healthy siblings

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**ABSTRACT**

**Objective:** This study aimed to investigate retinal abnormalities and their relationship with social cognitive function, and to assess whether retinal changes could be observed in the healthy siblings of patients with schizophrenia in a similar manner, suggesting their potential as an endophenotype.

**Method:** The study included 28 patients with schizophrenia, 28 of their siblings, and 28 healthy control subjects. Social cognition tests were administered, and measurements of the retinal nerve fiber layers (RNFL), ganglion cell layer plus inner plexiform layer (GCL+IPL), and cup volumes were obtained using optical coherence tomography (OCT).

**Results:** Analyses revealed no differences between the groups in RNFL thickness. The cup volume was significantly larger in both eyes of the patient group compared to the control group. The mean thickness of the GCL+IPL in the left eye was significantly lower in the patient group compared to the healthy control group, with a similar difference also observed between the siblings of patients and the control group. A statistically significant difference was found among all groups in the total scores of social cognition tests. A weak correlation was identified between retinal layer thicknesses and social cognition test scores in both the patient and sibling groups.

**Conclusion:** These findings suggest that GCL+IPL thickness can be a useful endophenotype for the early diagnosis of schizophrenia. While retinal changes do not predict cognitive symptoms in patients with schizophrenia, they may play an important role in identifying high-risk groups.

**Keywords:** Schizophrenia, optical coherence tomography, retina, social cognition, endophenotype

## INTRODUCTION

Schizophrenia is a severe mental disorder characterized by significant disturbances in thinking, perception, attention, affect, and behavior, along with profound losses in interpersonal relationships, adaptation to work and society, as well as delusions and hallucinations. One of the most significant outcomes of schizophrenia is poor functioning in patients (1). Social impairment generally worsens over the course of the disorder and is often resistant to antipsychotic treatment (1). A key aspect of social cognition is the ability to conceptualize other people's mental states, such as their beliefs and intentions,

**How to cite this article:** Akin F, Danaci AE, Kayikcioglu RO, Tasci MY. Retinal abnormalities and their relationship with social cognition in patients with schizophrenia and their healthy siblings. Dusunen Adam J Psychiatr Neurol Sci 2024;37:179-188.

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**Received:** May 04, 2024; **Revised:** September 17, 2024; **Accepted:** October 21, 2024

known as theory of mind. There is growing interest in understanding social cognition in individuals with schizophrenia (2). Difficulties in social cognition might directly contribute to impaired social functioning in these patients. The thalamus, an extension of the diencephalon, a subcortical structure located deep within the brain, plays a crucial role in sensory processing, motor control, and social cognitive functions. The Enhancing NeuroImaging Genetics through Meta-Analysis Schizophrenia Working Group (ENIGMA-SZ) has revealed that the volumes of the hippocampus, amygdala, thalamus, and nucleus accumbens (NA) were smaller in patients with schizophrenia compared to healthy controls (3). Volume reduction in subcortical structures such as the thalamus may impact social functioning (3).

In addition to volume reduction, schizophrenia is associated with significant impairments in various information processing areas, from early perceptive processing stages to higher-level complex cognitive functions. Studies on etiology have shown that some of these impairments are characterized by early visual abnormalities (4–6). Research has linked the severity of negative symptoms to low visual performance and demonstrated that higher performance scores in vision tests are paralleled by higher performance scores in neurocognitive and social cognition tests (7–9). Structural equation modeling analyses have shown that social cognition mediates the relationship between visual processing and social functioning in schizophrenia (10, 11). It has been suggested that visual processing and social cognitive skills are important components in the pathway to functional recovery in schizophrenia. Based on findings from brain volume reduction and neurophysiological studies, the retina, an extension of the diencephalon, has become a research focus over the last decade. With its ectodermal origin, the retina can be considered a unique anatomical model for the central nervous system. Several studies comparing patients with schizophrenia and healthy controls have reported a reduction in the retinal nerve fiber layer (RNFL) thickness in the patient group, (12, 13) particularly in the peripapillary RNFL thickness (14–16). However, a study involving patients in the early stages of schizophrenia (17) found no difference in retinal nerve fiber layer thickness between patients and controls. A meta-analysis indicated that the mean RNFL thickness in patients with schizophrenia was significantly reduced compared to healthy controls (18). Another study involving 26 patients with schizophrenia and schizoaffective disorders and a healthy group reported a negative correlation between illness duration and RNFL volume (19). A meta-analysis has also demonstrated a reduction in peripapillary RNFL and ganglion cell layer plus inner plexiform layer (GCL+IPL) thickness in patients with schizophrenia (20).

Research exploring the relationship between the retina and cognitive functions has shown that RNFL and GCL+IPL thicknesses are associated with the duration of illness and neurocognitive decline in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (21–24). To date, there is no study investigating the relationship between social cognition and optical coherence tomography (OCT). In addition to neurocognitive tests, a study in the literature supports the finding that the ability to distinguish the mother's face from other faces and to imitate it at an early age is present in newborns as early as 4-6 weeks (25).

An endophenotype approach was introduced based on the hypothesis that complex genetic disorders involve specific neurological function disorders, with a group of genes representing these disorders. Endophenotypes are defined as heritable and measurable traits related to illness that are more sensitive to the underlying biological mechanisms of a disorder than the broad clinical phenotype (26). For any phenotypic characteristic of a disorder to be accepted as an endophenotype, it must meet several conditions. These conditions include being more related to affected individuals than the general population, demonstrating genetic transmission, not being influenced by treatment, and being more common in healthy relatives than in the general population. Due to its ability to indirectly indicate cortical thickness and its association with early visual abnormalities, retinal changes emerge as a candidate for investigation as an endophenotype.

Considering the limited number of studies exploring retinal structure and function in schizophrenia, research involving OCT and including siblings becomes significant. Therefore, examining retinal changes in healthy siblings of patients may provide insights into the pathophysiological processes of a neurodevelopmental disorder such as schizophrenia. This study aims to investigate retinal changes in patients with schizophrenia and their unaffected healthy siblings and to identify potential endophenotypes and biomarkers that will contribute to understanding the biological foundation of

schizophrenia. The relationship between structural retinal changes and social cognition was also examined. We hypothesized that RNFL and GCL+IPL thickness would be lower, and cup volume would be larger in patients and their healthy siblings compared to the healthy control group. We also hypothesized that these retinal changes would correlate with impairments in social cognition.

## METHODS

Twenty-eight clinically stable patients diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) were recruited from the psychosis unit, along with 28 healthy siblings who met the inclusion and exclusion criteria. The patients had not experienced psychiatric hospitalization in the previous six months. For the control group, 28 healthy subjects matched with the study group in terms of age, gender, and duration of education were included. All tests were administered in a single session. The doses of antipsychotic therapy used by all patients were converted into chlorpromazine-equivalent doses. Visual acuity examinations and OCT measurements were conducted.

The exclusion criteria for all participants were as follows: a) any previous or concurrent systemic disease that could affect the eyes (including diseases, hyperlipidemia, hypertension, and cardiovascular diseases), b) any prior retinal or ocular pathology such as diabetic retinopathy, uveitis, glaucoma, cataracts, or macular degeneration, c) a history of ocular surgery or trauma, d) any neurological condition known to affect eyesight, e) glaucoma or myopia/hypermetropia (±4 D), and f) substance or alcohol abuse.

Participants in the control and healthy sibling groups who, based on their anamneses and medical health records, had any current and/or lifelong psychiatric or neurodevelopmental disorder, or a neurodegenerative diagnosis, were excluded from the study. Similarly, patients with other psychiatric comorbidities, neurodevelopmental, or neurodegenerative disorders were not included.

### Measures

*Positive and Negative Syndrome Scale (PANSS)*

The Positive and Negative Syndrome Scale is a semi-structured 30-item scale that measures the severity of positive, negative, and general symptoms in schizophrenia (27). It has been demonstrated that the Turkish version of PANSS is valid and reliable for assessing negative and positive syndromes and general psychopathology in samples of Turkish patients with schizophrenia (28).

*Eyes Test*

The Eyes Test measures an individual's ability to describe the mental state of a person by focusing solely on their eyes. The scale was developed by Baron-Cohen et al. in 1997 (29), and a 32-item version of the scale adapted to Turkish by Yildirim et al. (30) was used in this study. It is a performance-based test, and its reliability has been established.

*Facial Emotion Identification Test*

This test was developed by Kerr and Neale in 1993 (31). Its validity and reliability in the Turkish population were tested by Erol et al. in 2009 (32).

*Hinting Task*

The Hinting Task is one of the assessments used to evaluate the theory of mind subdomain of social cognition. In Turkiye, Bora et al. (33) used this task in their studies conducted in 2006.

*Optical Coherence Tomography*

The Zeiss Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Dublin, CA, USA) model was used in our center. All scans were performed by a single experienced operator. High-quality images were obtained using macular map and disk map protocols. Only images with a signal power greater than 25 dB and with full central focusing were included in the study. Optical nerve head (ONH) measurements involved six cycles of 6-mm linear scans with a radial configuration, each separated by a 30-degree angle. ONH data were obtained from the automatic identification of the optical nerve head margin defined by the OCT software. The ONH parameter evaluated in this study was the cup area/volume. Peripapillary OCT measurements were obtained from the average of three circular scans with a 3.4-mm diameter, centered on the optical nerve head. The parameter evaluated in this study was the mean RNFL. The mean GCL+IPL thickness was measured from 15 vertical sections, represented as lines within a 7 mm square area located 1 mm temporal to the central fovea. Macular thickness maps were automatically generated by the software after radial linear scans centered on the fovea. For the central macula volume, the measurements of the central macula segment with a 1-mm diameter and the surrounding area with a 3-mm diameter, obtained

**Table 1: Sociodemographic and clinical data**

| | P (n=28) | PS (n=28) | C (n=28) | p |
|---|---|---|---|---|
| Age, Mean±SD | 34.61±9.39 | 31.5±9.56 | 33.82±8.8 | 0.481 |
| Sex (female), n (%) | 12 (42.9) | 12 (42.9) | 10 (35.7) | 0.821 |
| Smokers, n (%) | 8 (28.6) | 12 (42.9) | 8 (28.6) | 0.424 |
| Length of education (years), Mean±SD | 11.89±3.08 | 12.54±2.90 | 12.79±2.43 | 0.486 |
| BMI (kg/m$^2$), Mean±SD | 29.1±5.5 | 25.3±3.9 | 26.1±4.8 | **0.010*** |
| Duration of disease (years), Mean±SD | 15.39±10.10 | – | – | – |
| CPZe (mg), Mean±SD | 637.86±400.68 | – | – | – |
| PANSS total score, Mean±SD | 44.93±10.90 | – | – | – |
| Inpatient treatment (last year), n (%) | 9 (32.1) | – | – | – |

SD: Standard deviation; P: Patients; PS: Patient siblings; C: Controls; BMI: Body mass index; PANSS: Positive and Negative Syndrome Scale; CPZe: Chlorpromazine equivalent dose; *Significant at p<0.05.

using the fast macula thickness measurement mode, were evaluated. Macular map and central macular thickness measurements were conducted, and macular thickness was calculated as the average thickness between the inner limiting membrane and the retinal pigment epithelium.

### Statistical Analysis

The data obtained from the study were analyzed using the SPSS version 22.0. No power analysis was conducted. The Shapiro-Wilk test was used to evaluate the normality of the numeric data. Numerical variables with normal distribution were presented as mean±standard deviation, while non-normally distributed variables were presented as median (minimum–maximum) values. The chi-square test was applied to compare the sociodemographic data. One-way analysis of variance (ANOVA) was used for parametric variables, and the Kruskal-Wallis test was used for non-parametric variables. When a difference was found between groups, the Tukey B test was applied as a post hoc test to identify the source of the difference (Bonferroni correction was not applied). The relationship between two numeric variables was assessed using the Pearson correlation test for normally distributed data and the Spearman rank correlation coefficient for non-parametric data. The level of statistical significance was set at p<0.05.

## RESULTS

### Sociodemographic and Clinical Data

The sample was divided into three groups: patients (P), patient siblings (PS), and controls (C). No significant differences were found between the groups in terms of mean age (p=0.834), gender distribution (p=0.822), smoking status (p=0.424), and length of education (p=0.486). However, the mean body mass index (BMI) (p=0.01), was higher in the patient group compared to the other two groups. The data related to the treatment background of the patient group indicated that the mean duration of illness was 15.39±10.10 years, and the chlorpromazine-equivalent dose was 637.86±400.68 mg. Nine (32.1%) patients were hospitalized in the last year. None of the patients who were hospitalized in the past year had been hospitalized within the last six months. The sociodemographic and clinical data are presented in Table 1.

### Comparison of Groups with Respect to Social Cognition Test Scores

There was a statistically significant difference between the groups in the total scores for the Eyes Test, Hinting Task, and Facial Emotion Identification Test (p=0.005; p<0.001; p=0.002). Post-hoc analyses showed that the total number of correct answers in the Eyes Test and the score obtained from the Hinting Task were highest in the control group. The total number of correct answers in the Eyes Test was higher (p=0.005) in the patient sibling group compared to the patient group and lower (p=0.001) compared to the control group, with the differences being statistically significant. Similarly, the Hinting Task score was higher (p<0.001) in the patient sibling group compared to the patient group and lower (p<0.001) compared to the control group, with the differences being statistically significant. The number of correct answers in the Facial Emotion Identification Test was statistically higher (p=0.003) in the patient sibling group compared to the patient group, but there was no significant difference with the control group (p=0.858). The mean social cognition test scores for the groups are shown in Table 2.

**Table 2: Mean social cognition test scores of groups**

| | P Mean±SD | PS Mean±SD | C Mean±SD | Test statistics | Post-Hoc |
|---|---|---|---|---|---|
| Total number of correct answers in Eyes Test | 18.20±5.85 | 22.03±3.86 | 25.10±2.75 | F=16.191 | P<PS p=**0.005*** |
| | | | | p=**0.005*** | P<C p<**0.001*** |
| | | | | | PS<C p=**0.001*** |
| Hinting task score | 10.23±4.37 | 17.43±2.59 | 19.53±0.81 | F=71.750 | P<PS p=**0.001*** |
| | | | | p=**0.001*** | P<C p<**0.001*** |
| | | | | | PS<C p<**0.001*** |
| Facial Emotion Identification Test score | 22.43±4.65 | 25.67±2.69 | 25.77±1.81 | F=8.706 | P<PS p=**0.003*** |
| | | | | p=**0.002*** | P<C p=**0.002*** |
| | | | | | PS, C p=0.858 |

SD: Standard deviation; P: Patients; PS: Patient siblings; C: Controls. One-way analysis of variance (ANOVA) results are shown in the row under F/p. *Indicates significance at p<0.05. A post-hoc Tukey test was used to explore pairwise differences. Significant results are indicated in the row under the post-hoc analysis. *Denotes significance at p<0.05.

**Table 3: Comparison of optical coherence tomography (OCT) measurements of groups**

| | P | | PS | | C | | $\chi^2$/p | Post-Hoc |
|---|---|---|---|---|---|---|---|---|
| | Mean±SD | Min–Max | Mean±SD | Min–Max | Mean±SD | Min–Max | | |
| Cup volume, R ($mm^3$) | 0.194±0.20 | 0.01–0.785 | 0.153±0.13 | 0.01–0.436 | 0.093±0.11 | 0.01–0.365 | 6.941 | P>C p=**0.010*** |
| | | | | | | | p=**0.013*** | PS>C p=**0.049*** |
| | | | | | | | | P, PS p=0.700 |
| Cup volume, L ($mm^3$) | 0.188±0.16 | 0.02–0.598 | 0.159±0.15 | 0.01–0.603 | 0.084±0.09 | 0.01–0.413 | 6.780 | P>C p=**0.010*** |
| | | | | | | | p=**0.034*** | PS, C p=0.081 |
| | | | | | | | | P, PS p=0.502 |
| GCL-IPL, R (μm) | 79.61±9.91 | 37–91 | 79.54±12.3 | 25–95 | 84.61±6.80 | 73–108 | 5.456 | – |
| | | | | | | | p=0.065 | |
| GCL-IPL, R (μm) | 78.64±13.3 | 31–91 | 81.64±6.18 | 72–95 | 85.32±6.64 | 75–106 | 6.087 | P<C p=**0.026*** |
| | | | | | | | p=**0.048*** | PS<C p=**0.042*** |
| | | | | | | | | P, PS p=0.902 |

SD: Standard deviation; P: Patients; PS: Patient siblings; C: Controls; GCL-IPL: Mean ganglion cell complexes thickness; R: Right eye; L: Left eye. Kruskal-Wallis test results are shown in the row under $X^2$/p. *Indicates significance at p<0.05. A post-hoc Mann-Whitney test was used to explore pairwise differences. Significant results are indicated in the row under the post-hoc analysis. *Denotes significance at p<0.05.

## OCT Data

Analyses of the right and left eye OCT measurements showed no significant difference between the three groups with respect to macular thickness parameters (p=0.338; p=0.910). Although the mean RNFL thickness was lower in the patient group compared to the control group in both eyes, the difference was not statistically significant (p=0.302; p=0.087, respectively). No statistically significant difference was observed between the three groups with respect to the RNFL superior, inferior, nasal, and temporal quadrant thickness parameters.

There was a significant difference between the three groups in the right and left eye cup volume measurements (p=0.013; p=0.034, respectively). A post-hoc analysis indicated that the cup volume was larger in the schizophrenia patient group compared to the control group and this result was statistically significant (right eye p=0.010; left eye p=0.010). Cup volume was also larger in the patient sibling group compared to the control group in the right eye (right eye p=0.049; left eye p=0.081). For the mean GCL+IPL thickness measurements, while there was no significant difference between the three groups for the right eye, a significant difference was found for the left eye (p=0.048). Post-hoc analysis showed that both the patient and patient sibling groups had significantly lower GCL+IPL thickness than the control group (p=0.026; p=0.042). The mean cup volumes and GCL+IPL measures with standard deviations for the schizophrenia, patient sibling, and control groups are reported in Table 3.

**Table 4: Correlation coefficients between social cognition tests and optical coherence tomography (OCT) measurements of the groups (r values)**

| | P | | | | PS | | | | C | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cup volume ($mm^3$) | | GCL-IPL (µm) | | Cup volume ($mm^3$) | | GCL-IPL (µm) | | Cup volume ($mm^3$) | | GCL-IPL (µm) | |
| | Right | Left | Right | Left | Right | Left | Right | Left | Right | Left | Right | Left |
| Total number of correct answers in Eyes Test | 0.22 | 0.12 | 0.23 | 0.03 | 0.04 | 0.02 | 0.20 | 0.03 | 0.13 | 0.09 | 0.02 | 0.09 |
| Facial Emotion Identification Test score | 0.10 | 0.03 | 0.22 | **0.42** | 0.04 | 0. 08 | 0.03 | 0.06 | 0.02 | 0.02 | 0.04 | 0.06 |
| Hinting Task score | 0.04 | 0.08 | 0.02 | 0.13 | 0.08 | 0.03 | 0.09 | 0.08 | 0.21 | 0.17 | 0.04 | 0.02 |

P: Patients; PS: Patient siblings; C: Controls. GCL-IPL: Mean ganglion cell complexes thickness. Significant correlation coefficient is indicated in bold type ($p<0.05$). Spearman correlation test was used to explore the relationship between social cognition tests and OCT measurements in the groups.

### Correlations Between Social Cognition Tests and OCT Measurements of the Groups

The correlation between the OCT measurements and the Eyes Test, Facial Emotion Identification Test, and Hinting Task in the patient, patient sibling, and control groups was reviewed. A moderately positive correlation was found in the patient group between the total score of the Facial Emotion Identification Test and the left eye GCL+IPL thickness ($r=0.421$, $p=0.026$). No correlation was found between the Hinting Task scores and any of the OCT measurements. In the patient sibling group, no correlation was observed between any social cognition test and OCT measurement. Similarly, no correlation was found between the social cognition tests and OCT measurements in the control group. The results are shown in Table 4.

## DISCUSSION

The purpose of this study was to compare the retinal layer thicknesses of patients with schizophrenia to those of the patient siblings and control groups and to investigate the relationship between retinal layer thicknesses and social cognition.

When examining social cognition studies, changes in the temporoparietal junction, medial prefrontal cortex, superior temporal gyrus/sulcus, anterior and posterior cingulate cortices, insula, precuneus, and amygdala have been consistently reported in structural neuroimaging studies (34). The thalamus, a subcortical structure located deep within the brain, plays a crucial role in sensory processing, motor control, and cognitive functions. Magnetic resonance imaging (MRI) studies have reported atrophy of the pineal gland, a part of the diencephalon, in patients with schizophrenia and individuals at high clinical risk of developing psychosis (35). The ENIGMA Schizophrenia Working Group revealed that the volumes of the hippocampus, amygdala, thalamus, and nucleus accumbens were smaller in patients with schizophrenia than in healthy controls (3). Volume reduction of subcortical structures such as the thalamus may impact social functioning (3). Although there are no studies specifically on the relationship between social cognition and retinal structure, some studies have examined neurocognition and the retina. A recent study found that cognitive functions such as immediate memory and visuospatial functions were associated with reductions in RNFL thickness (36). Another study observed significant reductions in peripapillary RNFL in patients with low Montreal Cognitive Assessment (MoCA) scores (37).

Several studies have reported a statistically significant reduction in RNFL thickness, particularly in patients with chronic, refractory schizophrenia (12, 13, 17), while other studies have found no differences (38–40). Recent data from studies using OCT measurements of retinal layer thickness appear contradictory due to methodological differences. Many studies investigating neurodegenerative diseases have shown that RNFL thickness is associated with both cortical thinning and cognitive performance (41). The inconsistencies in these studies are argued to have originated from the failure to adequately exclude eye diseases, such as glaucoma, myopia, and hypermetropia, as well as metabolic diseases, such as diabetes mellitus and hypertension, which can affect RNFL thickness (38, 42). In our study, no significant difference was found between the groups in terms of RNFL thickness and macular thickness. Our findings differ from some previous studies. These discrepancies may be explained by the presence of BMI differences between the groups and the fact that diseases such as hypertension and diabetes mellitus were excluded based solely on patient statements in our study. As discussed earlier, the results in the literature are not

fully consistent. Differences between studies may be attributed to the use of different OCT devices with lower resolution or the inadequate control of systemic diseases. Ascaso et al. (12) found a reduction in RNFL thickness in patients who had not experienced an acute episode in the last six months compared to controls. However, the RNFL thickness of patients who had a recent episode did not differ from that of the control group, suggesting that the inflammatory processes during an acute episode could have been suppressing retinal layer reduction. In our patient group, nine (32.1%) patients had not been hospitalized in the last six months but were hospitalized in the last year. This may explain why there was no observed difference in RNFL measurements between the patient and the control groups in our study.

There is only one recent study on cup volume. In this study conducted by Silverstein et al. (38), no significant difference was found between patients and the healthy control group regarding macular volume, macular thickness, and RNFL measurements when confounding factors such as medical comorbidity and age were controlled. However, cup volume expansion was observed in both groups, and it was argued that this may have been due to insufficiently controlled metabolic diseases. The reason for this cup volume expansion is axonal tissue loss. Conditions such as glaucoma, chronic diseases causing hypoglycemic, hypoxic, and ischemic damage, and atherosclerosis may lead to an enlarged cup volume. Similar to this single study in the literature, our study also found an enlarged cup volume in both eyes of the patient group compared to the control group. This may have been due to the pathophysiology of schizophrenia, but it may also have been caused by vascular pathologies we were unable to control, other metabolic diseases leading to ischemic damage that we could not adequately exclude, or the metabolic side effects of antipsychotic medications. The design of our study does not provide a satisfactory explanation for this question. Further research on cup volume in first-episode patients who have not used antipsychotics may clarify this issue. In this study, the cup volume was significantly larger in both eyes of the patient group compared to the control group. This outcome may have been influenced by confounding factors such as non-homogeneous myopia/hypermetropia values that may affect cup volume, differences in age range among siblings despite attempts to control for it, lack of comparison of optical disk sizes, or vascular pathologies in the patient siblings group that we could not control. For instance, while patients with major retinal complications such as diabetic retinopathy were excluded, those with minor retinal changes may not have been excluded. Therefore, there is a need for further studies where these confounding factors are controlled individually.

Reviewing the literature on GCL+IPL thickness reveals that studies on this topic are relatively new and limited in number. In the study by Celik et al. (39), which was the first to investigate GCL+IPL thickness, it was found that GCL+IPL volume was lower in the patient group compared to the control group. Kurtulmus et al. (43) also reported that IPL thickness was lower in both the patient and healthy first-degree relative groups compared to the control group. In a recent study, GCL+IPL thickness was found to be lower in the schizophrenia patient group compared to the control group. In the same study, strong correlations were shown between neurocognitive tests and OCT findings in both the patient group and healthy sibling group (44). Similarly, in our study, a statistically significant difference was found between the groups in the mean GCL+IPL thickness measurements of the left eye. Post-hoc analysis indicated that GCL+IPL thickness was significantly lower in both the patient and patient sibling groups compared to the control group. Explaining potential differences between the two eyes is limited by current knowledge. Previous studies have also reported differences between quadrants (14, 17, 43).

Most studies on the relationship between OCT and cognitive functions seem to focus on neurological diseases. Our study demonstrated performance differences in social cognition tests among the patient siblings, schizophrenia, and control groups. In the same study, strong correlations were shown between neurocognitive tests and OCT findings in both the patient group and the healthy sibling group (44). In this regard, we believe our sample group represents cognitive function disorders well. Data from these studies indicate that OCT measurements correlate with MRI findings, particularly in patients with Alzheimer's disease and multiple sclerosis, and that both RNFL and GCL+IPL are associated with cognitive performance (23, 45). Studies on OCT and cognitive function have not been limited to patient groups but have also included healthy populations (22). A study involving older adults aged 60 to 80 years demonstrated that a decrease in GCL+IPL thickness was associated with reduced gray matter volume, especially in the occipital and temporal lobes, and that GCL+IPL thickness was a

marker for neurodegeneration (46). Our study found a positive but weak correlation between the facial emotion identification test and GCL+IPL thickness in the patient group; no correlations were found with any social cognition test in the patient sibling and control groups. There was either a weak or no correlation between social cognition and OCT measurements in all three groups. Reviewing the literature, we find that the relationship between retinal measurements and cognitive disorders has been more extensively investigated in neurological diseases. In particular, in neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, and mild cognitive disorders, gray matter volume measurements have been considered very important biomarkers for identifying neuronal loss and tracking the progression of cognitive decline (41). Many studies investigating neurodegenerative diseases have shown that both RNFL and GCL+IPL thicknesses are associated with cognitive performance. Recent studies have demonstrated that a reduction in the area where cell bodies and dendrites reside occurs before retinal ganglion cell death and loss; thus, GCL+IPL may be more vulnerable to damage than RNFL [41]. It is also known that GCL+IPL thickness is less affected by individual variations compared to RNFL thickness (47).

Our study has several limitations. First, although the sample sizes in the three groups were similar, the relatively small number of participants (28 per group) may have resulted in some tests possibly lacking sufficient power. Therefore, they may not be adequate for detecting differences between the groups with respect to the other OCT parameters. The sample sizes consisted of a heterogeneous group, and the exclusion criteria for the healthy siblings and control group were based on self-report rather than being verified using Structured Clinical Interview for DSM (SCID). Another limitation is that the OCT device used did not allow for the measurement of single-layer ganglion cell layer (GCL) or interior plexiform layer (IPL); only a cumulative measurement of the ganglion cell complex (GCL+IPL) was possible. Future studies might benefit from separate measurements of the ganglion cell complex. The major limitation of our study is that it was cross-sectional. Longitudinal follow-up studies, with regular OCT scans starting from the early stages of the disorder, are needed to provide more accurate data on disorder progression. Additionally, it was not possible to exclude the effect of antipsychotic use on the parameters studied in patients with schizophrenia. All participants (100%) were on typical or atypical antipsychotic therapy. Drugs classified as antipsychotic medications are known to have effects at different receptor levels, but their impact on retinal changes is not known. The absence of studies in the literature examining the effect of antipsychotic drugs on retinal layer thickness makes it difficult to interpret the results in a group with such varied treatment regimens.

## CONCLUSION

For neurodevelopmental disorders such as schizophrenia, studies involving healthy siblings who share similar genetic predispositions to patients but have not been affected by the disorder and its related complications are important. Our study is one of the few sibling studies in the literature. Our results support the findings of Kurtulmus et al. (43), which involved first-degree relatives. Therefore, it aims to contribute to the literature by supporting studies on the neurodevelopmental hypothesis of schizophrenia. According to the results of our study, a significant difference was found between the three groups in mean GCL+IPL thickness measurements for the left eye. GCL+IPL thickness was statistically lower in both the patient and patient sibling groups compared to the control group. In this sense, this finding appears consistent with the few studies in the literature and contributes by reinforcing previous results. The GCL+IPL is composed of cell bodies and dendrites, and for this reason, it is believed to reflect synaptic pruning, which is thought to play a role in the etiology of schizophrenia.

Our study provides evidence that these results, observed in healthy siblings as well, may reflect the abnormal synaptic/dendritic organization in schizophrenia and synaptic pruning, GCL+IPL thickness a potential endophenotype candidate. This study is the first study to explore the relationship between retinal layer changes and social cognition in patients with schizophrenia and their unaffected siblings. However, no strong correlation was found between retinal layer thicknesses and social cognition in any of the three groups. Reviewing the literature, more studies exist in the neurocognitive area, and we can say that there is a need for further research in social cognition. Based on our results, there is not yet sufficient evidence to use retinal changes for assessing cognitive functions. Therefore, investigations should continue to determine whether structural retinal layer changes in patients with schizophrenia could play an important role in identifying high-risk groups. Future OCT-based retinal studies may help identify biomarkers

that facilitate understanding the biological basis of psychosis and aid in the prevention, diagnosis, and treatment of schizophrenia. Similar studies could also explore the relationship between structural retinal layer changes and social cognition or neurocognition, thereby clarifying the role of the peripheral nervous system in the etiology of schizophrenia.

| Contribution Categories | | Author Initials |
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| Category 1 | Concept/Design | F.A., A.E.D., R.O.K. |
| | Data acquisition | F.A., A.E.D., R.O.K. |
| | Data analysis/Interpretation | F.A., A.E.D., M.Y.T. |
| Category 2 | Drafting manuscript | F.A., A.E.D., R.O.K. |
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**Acknowledgements:** We thank Associate Professor Dr. Orkun Aydin for his comments and editing that greatly improved the manuscript.

**Ethical Approval:** The Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee granted approval for this study (date: 11.03.2020, number: 1/17).

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Informed Consent:** Informed consent was obtained from all participants.

**Use of AI for Writing Assistance:** Not declared.

**Financial Disclosure:** Support and funding was provided by Celal Bayar University Scientific Research Projects Unit (BAP) (Project no: 2020-062).

**Peer-review:** Externally peer-reviewed.

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