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Original Article

Retinal Structural Alterations and Functional Outcomes in Schizophrenia: An Optical Coherence Tomography Study

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Abstract

Background: Retinal structural alterations have increasingly been investigated as potential peripheral indicators of neurobiological changes in schizophrenia (SCZ). However, the relationship between retinal thickness and clinically relevant outcomes, particularly functional recovery and disability, remains insufficiently understood. This study aimed to compare retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thicknesses assessed using optical coherence tomography (OCT) between patients with SCZ and healthy controls (HC) and to examine their associations with psychopathology severity, functional recovery, and disability. **Methods:** This cross-sectional comparative study included 65 clinically stable patients with SCZ aged 40 years or younger who were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and 65 HC without a current or lifetime psychiatric disorder. RNFL and GCC thicknesses were assessed using OCT. Psychopathology severity, functional recovery, and disability were assessed using the Positive and Negative Syndrome Scale (PANSS), Functional Recovery Scale in Schizophrenia (FRSS), and World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), respectively. **Results:** After adjustment for age and years of education, GCC thickness was significantly lower in patients with SCZ than in HC ($F = 7.70$, $p = 0.006$). The overall group effect for RNFL thickness was not significant ($F = 1.87$, $p = 0.174$); however, the group × RNFL region interaction was significant ($F = 3.83$, $p = 0.010$), although none of the region-specific group comparisons remained significant after Holm correction for multiple comparisons. No significant correlations were observed between regional OCT parameters and psychopathology severity, functional recovery, or disability. In bootstrap multiple regression analyses, higher PANSS total scores were independently associated with lower FRSS scores ($B = -0.273$, bootstrap 95% CI = −0.357 to −0.172, $p < 0.001$) and higher WHODAS 2.0 scores ($B = 0.222$, bootstrap 95% CI = 0.097 to 0.357, $p = 0.001$), whereas none of the regional GCC or RNFL thickness measures was independently associated with either outcome. **Conclusions:** OCT may help identify retinal structural alterations in clinically stable patients with SCZ. However, retinal thickness measurements were not associated with psychopathology severity, functional recovery, or disability and appeared insufficient to explain individual functional outcomes, whereas overall psychopathology severity remained closely associated with functioning.

Keywords: schizophrenia; optical coherence tomography; retinal nerve fiber layer; ganglion cell complex; functional recovery; disability

Main Points

1. Patients with schizophrenia had significantly lower ganglion cell complex thickness than healthy controls after adjustment for age and years of education.

2. Although the overall group effect for retinal nerve fiber layer thickness was not significant, group differences varied by retinal region; however, none of the region-specific group comparisons remained significant after Holm correction for multiple comparisons.

3. Ganglion cell complex and retinal nerve fiber layer measurements were not significantly associated with symptom severity, functional recovery, or disability in the patient group.

4. Greater overall psychopathology severity was independently associated with poorer functional recovery and greater disability, whereas retinal structural measurements did not independently contribute to these outcomes.

5. Optical coherence tomography may be useful for detecting group-level retinal structural alterations in schizophrenia. However, retinal thickness measurements alone appear insufficient to explain individual differences in functional recovery and disability.

1. Introduction

Schizophrenia (SCZ) is a severe mental disorder that affects more than 23 million people worldwide and substantially impairs quality of life [1]. SCZ is characterized by disturbances in thought, perception, and behavior, including hallucinations, delusions, disorganized speech, and disorganized behavior [2]. Cognitive impairments involving memory, attention, executive functioning, and process-

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ing speed may adversely affect social relationships, occupational functioning, and activities of daily living [3]. Accordingly, the burden of SCZ extends beyond psychotic symptoms and includes persistent functional impairment and disability [4].

Historically, treatment success in schizophrenia has been defined primarily in terms of reducing or eliminating acute psychotic symptoms. However, contemporary clinical approaches recognize that symptomatic remission does not necessarily translate into functional recovery [5]. Functional recovery is a multidimensional construct encompassing independence, activities of daily living, social relationships, occupational functioning, and community participation [6]. Consequently, functional impairment may persist in patients with SCZ despite substantial symptomatic improvement [4].

Disability in SCZ is increasingly recognized as a multidimensional construct associated with cognitive impairment, negative symptoms, impaired social functioning, and limitations in activities of daily living [4]. Therefore, identifying clinical and biological factors associated with functional recovery and disability may improve the assessment of patients' needs and inform individualized clinical management.

Although SCZ has traditionally been conceptualized as a neurodevelopmental disorder, neuroimaging and postmortem findings suggest that progressive neurobiological alterations may also contribute to its clinical course [7]. Neuroimaging studies have identified reductions in gray matter volume, particularly in frontal, temporal, and cingulate regions, together with ventricular enlargement in patients with SCZ [8]. Some of these structural alterations may be detectable during the early stages of illness and may progress over time [8]. At the cellular and molecular levels, these macroscopic alterations may be accompanied by reduced synaptic density, dendritic abnormalities, impaired neuronal connectivity, aberrant synaptic pruning, oxidative stress, and neuroinflammatory processes [9,10].

The retina shares a common embryological origin with the brain and contains highly organized neural layers and synaptic connections. It is therefore regarded as an accessible extension of the central nervous system. Retinal imaging may thus provide an indirect means of investigating structural alterations associated with central nervous system disorders [11]. Optical coherence tomography (OCT) enables quantitative assessment of retinal structures, including the retinal nerve fiber layer (RNFL), ganglion cell complex (GCC), macular thickness, and choroid [12]. OCT may therefore serve as a noninvasive and reproducible method for examining retinal correlates of central nervous system alterations in neurodegenerative and neuropsychiatric disorders [13].

Recent OCT studies and meta-analyses have shown that patients with SCZ have lower peripapillary RNFL, macular, and ganglion cell-inner plexiform layer thicknesses than healthy controls (HC) [14]. These findings suggest that retinal structural alterations may accompany the neurobiological changes associated with SCZ. Although previous studies have examined associations between OCT findings and psychopathology severity, cognitive performance, and clinical characteristics, the relationship between retinal structural alterations and functional recovery or disability remains insufficiently understood. Most of the available literature has focused on diagnostic group differences and symptom severity, whereas functional recovery and disability have received comparatively limited attention.

The primary objective of this study was to compare RNFL and GCC thicknesses, as measured by OCT, between clinically stable patients with SCZ and HC. The secondary objective was to examine the associations of RNFL and GCC thicknesses with psychopathology severity, functional recovery, and disability in the patient group and to assess whether these retinal parameters were independently associated with functional outcomes. We hypothesized that RNFL and GCC thicknesses would be lower in patients with SCZ than in HC and that lower retinal thicknesses would be associated with greater psychopathology severity and disability and poorer functional recovery. We further hypothesized that RNFL and GCC thicknesses would remain independently associated with functional recovery and disability after adjustment for age, illness duration, and psychopathology severity. By addressing these associations, this study aimed to clarify the potential value of OCT-derived retinal measurements as candidate biomarkers of functional outcomes in SCZ.

2. Materials and Methods

This cross-sectional comparative study was conducted between September 1, 2025, and March 1, 2026, at the Psychiatry and Ophthalmology outpatient clinics of Malatya Training and Research Hospital. Ethical approval was obtained from the Malatya Turgut Özal University Health Sciences Scientific Research Ethics Committee before participant recruitment (Decision No. 2025/254, dated July 30, 2025). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments. All participants received detailed information regarding the purpose and procedures of the study, and written informed consent was obtained before participation.

2.1 Participants

The patient group comprised 65 outpatients aged 40 years or younger who had been diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and were in a clinically stable phase. Eligible patients presenting consecutively to the Psychiatry Outpatient Clinic during the study period were invited to participate and were recruited after

providing written informed consent. The diagnosis of SCZ and the assessment of clinical stability were performed by an experienced psychiatrist. Clinical stability was operationally defined as the absence of psychiatric hospitalization, clinically significant psychotic exacerbation, or a major change in treatment during the preceding six months.

The control group comprised 65 volunteers aged 40 years or younger with no current or lifetime history of a psychiatric disorder. Eligible volunteers presenting consecutively to the Ophthalmology Outpatient Clinic for routine eye examination during the study period were invited to participate. Participants in the control group had no current or lifetime history of a psychiatric disorder. The absence of psychiatric disorders was confirmed through a clinical psychiatric evaluation performed by an experienced psychiatrist. All participants were required to have sufficient cognitive and communicative capacity to understand the study procedures and complete the assessments.

General exclusion criteria included intellectual disability, a neurological disorder, alcohol or other substance use, including cannabis use, and systemic conditions that could affect retinal or vascular structures, including diabetes mellitus and hypertension. Patients with SCZ were additionally excluded if they had any current psychiatric disorder other than SCZ. Smoking within 24 hours before OCT imaging was considered an exclusion criterion.

Ophthalmological exclusion criteria included a clinically significant refractive error, macular hole, cystoid macular edema, epiretinal membrane, vitreomacular traction, media opacity, vitreous hemorrhage, uveitis, choroidal neovascularization, diabetic maculopathy or retinopathy, and any other ocular disorder that could affect retinal measurements. Participants with a history of vitreoretinal surgery, cataract or glaucoma surgery, intravitreal injection, macular laser photocoagulation, or any other intraocular procedure were excluded. OCT images with inadequate signal quality, motion artifacts, or segmentation errors were not included in the analyses.

During the study period, 84 patients presenting consecutively to the Psychiatry Outpatient Clinic were screened for eligibility. Nineteen patients were excluded: four were older than 40 years, three did not meet the clinical stability criteria, five had a comorbid psychiatric disorder, including an alcohol or other substance use disorder, two had a neurological or systemic condition that could affect retinal measurements, two met an ophthalmological exclusion criterion, two had OCT images of inadequate quality, and one declined participation or did not complete the assessments. The remaining 65 patients with SCZ were included in the final analyses.

During the same period, 88 volunteers presenting consecutively to the Ophthalmology Outpatient Clinic for routine eye examination were screened as potential controls. Twenty-three volunteers were excluded: three were older than 40 years, three had a current or lifetime psychiatric disorder, four had a neurological or systemic condition that could affect retinal measurements, seven met an ophthalmological exclusion criterion, three had OCT images of inadequate quality, and three declined participation or did not complete the assessments. The remaining 65 participants constituted the HC group.

Power Analysis

The sample size was determined using an a priori power analysis based on a two-tailed independent-samples *t*-test comparing two independent groups. The analysis was performed using G*Power version 3.1 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany), assuming a medium effect size (Cohen's $d = 0.50$), an α level of 0.05, a statistical power of 80%, and a 1:1 allocation ratio. The analysis indicated that at least 64 participants per group, corresponding to a minimum total sample size of 128, were required. The final sample comprised 130 participants, including 65 patients with SCZ and 65 HC.

2.2 Procedure

After written informed consent was obtained, all participants underwent an eligibility assessment based on the psychiatric, medical, and ophthalmological inclusion and exclusion criteria. Sociodemographic characteristics, smoking and alcohol use, medical history, and family history of psychiatric disorders were recorded for all participants. For patients with SCZ, additional clinical information, including illness duration and number of psychiatric hospitalizations, was obtained.

The Positive and Negative Syndrome Scale (PANSS), Functional Recovery Scale in Schizophrenia (FRSS), and World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) were administered to patients with SCZ by an experienced psychiatrist during a face-to-face clinical interview. The control participants underwent a psychiatric evaluation to confirm the absence of current or lifetime psychiatric disorders but were not administered the clinical scales used in the patient group. Following the psychiatric assessment, all eligible participants underwent a detailed ophthalmological examination and OCT imaging using the standardized protocol described below. Psychiatric assessments and OCT imaging were completed on the same day.

2.3 Data Collection Instruments

2.3.1 Sociodemographic and Clinical Data Form

Participants' sociodemographic characteristics, smoking and alcohol use, medical history, and family history of psychiatric disorders were recorded using a form developed by the researchers. For the patient group, additional clinical variables included duration of illness, number of psychiatric hospitalizations, history of psychotic episodes, medication adherence, and perceived social support.

2.3.2 Positive and Negative Syndrome Scale (PANSS)

The PANSS is a semi-structured clinical interview scale developed by Kay et al. [15] to assess psychopathology severity in patients with SCZ. The scale consists of 30 items, each rated from 1 to 7. It comprises a seven-item positive syndrome subscale, a seven-item negative syndrome subscale, and a 16-item general psychopathology subscale. Higher scores indicate greater psychopathology severity. The validity and reliability of the Turkish version were established by Kostakoglu et al. [16]. Cronbach's α coefficients were reported as 0.75 for the positive syndrome subscale, 0.77 for the negative syndrome subscale, and 0.71 for the general psychopathology subscale.

2.3.3 Functional Recovery Scale in Schizophrenia (FRSS)

The FRSS is a clinician-rated instrument used to assess functional recovery in patients with schizophrenia. The scale is the Turkish adaptation of the Functional Remission of General Schizophrenia Scale (FROGS), originally developed by Llorca et al. [17]. The Turkish validity and reliability study was conducted by Emiroğlu [18]. The scale comprises 19 items rated on a 7-point Likert scale and assesses functional recovery in domains including personal care, social relationships, occupational functioning, and independent living. Assessments are based on clinical observations and interviews with the patient. Higher scores indicate better functional recovery. Cronbach's α for the Turkish version was reported as 0.890 [18].

2.3.4 World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)

The WHODAS 2.0 is a 36-item, semi-structured interview-based instrument that assesses difficulties experienced in daily functioning during the preceding 30 days, irrespective of the underlying medical diagnosis. It evaluates six domains: cognition, mobility, self-care, getting along, life activities, and participation. Items are rated on a 5-point Likert scale, with higher scores indicating greater disability. The validity and reliability of the Turkish version in patients with schizophrenia were established by Uluğ et al. [19]. Cronbach's α for the total scale was reported as 0.92.

2.3.5 Optical Coherence Tomography Imaging Protocol and Analysis

Retinal measurements were obtained using a spectral-domain optical coherence tomography device (SD-OCT; RS-3000 Advance, NIDEK Co., Ltd., Gamagori, Aichi, Japan). Before OCT imaging, all participants underwent a detailed ophthalmological examination performed by an experienced ophthalmologist.

RNFL thickness was assessed in the temporal, nasal, superior, and inferior quadrants using a 3.45-mm-diameter circular scanning protocol centered on the optic disc. For the present study, superior, inferior, temporal, and nasal RNFL thickness measurements were included in the analyses. GCC thickness was obtained from a 9 × 9-mm macular scanning area centered on the fovea and was recorded separately for the superior and inferior sectors. All RNFL and GCC measurements were obtained using the device's automated segmentation software.

All imaging was performed using the same device and a standardized acquisition protocol. To minimize potential diurnal variation, all OCT examinations were performed between 11:00 a.m. and 1:00 p.m. Only images with an SSI of ≥7/10, without motion artifacts or segmentation errors, were included in the analyses. Participants with ocular pathologies that could affect retinal measurements, those with a history of intraocular surgery or procedures, and those for whom adequate image quality could not be obtained were excluded from the study.

All OCT measurements were performed by an experienced ophthalmologist who was blinded to the participants' clinical and psychometric characteristics. Both eyes were evaluated separately, and RNFL and GCC measurements obtained from the right and left eyes were included in the statistical analyses.

2.4 Statistical Analysis

Statistical analyses were performed using jamovi (version 2.4.11; The jamovi project, Sydney, Australia) and JASP (version 0.19.3; JASP Team, University of Amsterdam, Amsterdam, the Netherlands). Categorical variables were presented as counts and percentages, whereas continuous variables were presented as means and standard deviations. The distributional characteristics of continuous variables were assessed using the Shapiro-Wilk test together with skewness and kurtosis values.

Sociodemographic and clinical characteristics were summarized using descriptive statistics. Continuous variables were compared between the patient and control groups using the independent-samples *t*-test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Effect sizes were calculated as Cohen's *d* for continuous variables and Cramér's V for categorical variables.

Because measurements were obtained from both eyes and from multiple measurements within each eye, linear mixed-effects models with a participant-specific random intercept were used to account for within-participant correlations. Separate models were fitted for GCC and RNFL thicknesses. In the GCC model, group, eye, and GCC sector (superior and inferior) were entered as fixed effects. The group × eye, group × GCC sector, eye × GCC sector, and group × eye × GCC sector interaction terms were also included. In the RNFL model, group, eye, and RNFL region (superior, inferior, temporal, and nasal) were entered as fixed effects. The group × eye, group × RNFL region, eye × RNFL region, and group × eye × RNFL region interaction terms were also included. Because the patient and

control groups differed significantly in age and years of education, both variables were included as covariates.

Model parameters were estimated using restricted maximum likelihood. Model assumptions were assessed by examining residual diagnostic plots for normality and homoscedasticity. Adjusted estimated marginal means for group, eye, and retinal region were calculated and reported with 95% confidence intervals. Model fit was evaluated using the intraclass correlation coefficient (ICC) and conditional R^2.

Within the patient group, associations between OCT parameters and psychometric scale scores were examined using Spearman's rank correlation coefficients because some variables deviated from normality. OCT parameters included mean superior and inferior GCC thicknesses and mean superior, inferior, temporal, and nasal RNFL thicknesses, with each regional value calculated as the mean of the corresponding right- and left-eye measurements. Psychometric measures included PANSS positive syndrome, negative syndrome, general psychopathology, and total scores, FRSS total score, and WHODAS 2.0 total score.

Bootstrap multiple linear regression analyses were conducted to identify variables independently associated with FRSS and WHODAS 2.0 total scores. Age, duration of illness, PANSS total score, mean superior and inferior GCC thicknesses, and mean superior, inferior, temporal, and nasal RNFL thicknesses were entered simultaneously into each model. For each GCC and RNFL region, the mean thickness was calculated by averaging the corresponding measurements from the right and left eyes. Bootstrap estimates of the unstandardized regression coefficients, standard errors, p values, and bias-corrected and accelerated (BCa) 95% confidence intervals were obtained using 5000 resamples. Multicollinearity was assessed using the variance inflation factor (VIF), with values greater than 5 considered indicative of problematic multicollinearity. All statistical tests were two-sided, and statistical significance was set at $p < 0.05$.

3. Results

3.1 Sociodemographic and Clinical Characteristics

The sociodemographic characteristics of the patient and control groups, between-group comparisons, and clinical characteristics of the patient group are presented in Table 1. No statistically significant differences were observed between the groups in terms of sex, marital status, employment status, place of residence, or smoking status (all $p >$ 0.05).

A family history of psychiatric disorders was significantly more frequent among patients with SCZ than among HC (27.7% vs. 1.5%; $\chi^2 = 17.814$, $p < 0.001$, Cramér's V = 0.370). Patients with SCZ were significantly older than HC (34.25 ± 7.09 vs. 26.69 ± 5.14 years; $t = 6.953$, $p < 0.001$, Cohen's $d = 1.22$) and had significantly fewer years of education (11.12 ± 3.27 vs. 12.95 ± 2.09 years; $t = -3.803$, $p < 0.001$, Cohen's $d = 0.67$). Therefore, age and years of education were included as covariates in the subsequent between-group analyses.

Among patients with SCZ, the mean duration of illness was 11.17 ± 6.98 years, and the mean number of psychiatric hospitalizations was 3.85 ± 5.24.

3.2 Retinal Ganglion Cell Complex Thickness

The linear mixed-effects model results and adjusted estimated marginal means for GCC thickness are presented in Table 2, and the sector-specific distribution of adjusted GCC thickness according to group is shown in Fig. 1. After adjustment for age and years of education, the main effect of group was statistically significant ($F = 7.70$, $p = 0.006$). Adjusted GCC thickness was higher in HC than in patients with SCZ (101.4 ± 1.09 µm vs. 96.7 ± 1.09 µm; B = 4.67, 95% CI = 1.37 to 7.96).

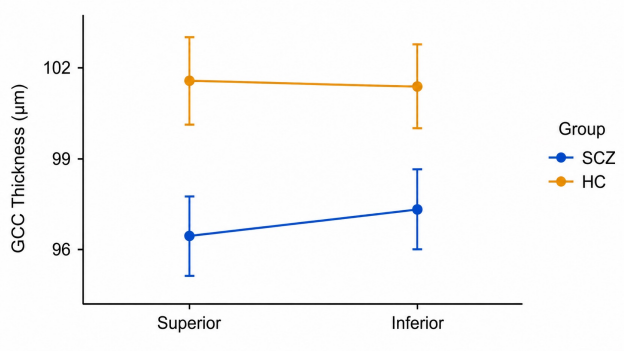


Fig 1. Adjusted estimated marginal GCC thicknesses by macular sector in patients with schizophrenia and healthy controls. Points represent adjusted estimated marginal means obtained from a linear mixed-effects model with a participant-specific random intercept, adjusted for age and years of education. Error bars indicate standard errors. Each group included 65 participants.

The main effect of eye was not statistically significant (F = 0.35, $p = 0.557$), with comparable adjusted GCC thicknesses in the right and left eyes (98.9 ± 0.75 µm vs. 99.2 ± 0.75 µm, respectively). In contrast, the main effect of GCC sector was statistically significant (F = 16.80, $p < 0.001$). Adjusted GCC thickness was higher in the inferior sector than in the superior sector (100.1 ± 0.75 µm vs. 98.0 ± 0.75 µm; B = 2.09, 95% CI = 1.09 to 3.09). Age (F = 0.04, $p = 0.850$) and years of education (F = 3.69, $p = 0.057$) were not significantly associated with GCC thickness.

None of the interaction effects reached statistical significance: group × eye (F = 0.76, $p = 0.383$), group × GCC sector (F = 0.90, $p = 0.343$), eye × GCC sector (F = 3.27, $p = 0.071$), or group × eye × GCC sector (F = 0.46, $p = 0.498$). The participant-level random-intercept variance was 55.4,

Table 1. Sociodemographic characteristics of the patient and control groups and clinical characteristics of the patient group.

Variable	Category	Patients with SCZ (n = 65) n (%)	HC (n = 65) n (%)	Test statistic	*p*	Effect size
Sex	Female	14 (21.5)	24 (36.9)	3.719	0.054	0.169
	Male	51 (78.5)	41 (63.1)			
Marital status	Single	51 (78.5)	42 (64.6)	3.060	0.080	0.153
	Married	14 (21.5)	23 (35.4)			
Employment status	Not employed	43 (66.2)	42 (64.6)	0.034	0.854	0.016
	Employed	22 (33.8)	23 (35.4)			
Place of residence	Provincial center	51 (78.5)	49 (75.4)	0.173	0.677	0.037
	Smaller settlement	14 (21.5)	16 (24.6)			
Family history of psychiatric disorders	No	47 (72.3)	64 (98.5)	17.814	**<0.001**	0.370
	Yes	18 (27.7)	1 (1.5)			
Smoking status	Non-smoker	31 (47.7)	41 (63.1)	3.113	0.078	0.155
	Smoker	34 (52.3)	24 (36.9)			
Variable		**Mean ± SD**	**Mean ± SD**	**T**	***p***	**Effect size**
Age (years)		34.25 ± 7.09	26.69 ± 5.14	6.953	**<0.001**	1.220
Years of education		11.12 ± 3.27	12.95 ± 2.09	–3.803	**<0.001**	0.670
Duration of illness (years)		11.17 ± 6.98	—	—	—	—
Number of hospitalizations		3.85 ± 5.24	—	—	—	—

Note: Data are presented as *n* (%) for categorical variables and mean ± SD for continuous variables. Categorical variables were compared using Pearson's chi-square test, and continuous variables were compared using the independent-samples *t*-test. Effect sizes were calculated using Cramér's V for categorical variables and Cohen's *d* for continuous variables. Cohen's *d* values are presented as absolute values. Duration of illness and number of hospitalizations were assessed only in the patient group. Statistically significant *p* values are shown in bold. Abbreviations: HC, healthy controls; SCZ, schizophrenia; SD, standard deviation.

the residual variance was 33.9, the intraclass correlation coefficient was 0.62, and the conditional R^2 was 0.661.

3.3 Retinal Nerve Fiber Layer Thickness

The linear mixed-effects model results and adjusted estimated marginal means for RNFL thickness are presented in Table 3, and the regional distribution of adjusted RNFL thickness according to group is shown in Fig. 2. After adjustment for age and years of education, the main effect of group was not statistically significant (F = 1.87, p = 0.174). Adjusted RNFL thickness was 103.0 ± 1.46 µm in HC and 100.0 ± 1.46 µm in patients with SCZ (B = 3.07, 95% CI = −1.33 to 7.46). The main effect of eye was also not statistically significant (F <0.01, p = 0.997), with comparable adjusted RNFL thickness in the right and left eyes (102.0 ± 1.08 µm vs. 102.0 ± 1.08 µm).

In contrast, the main effect of RNFL measurement was statistically significant (F = 877.60, p < 0.001). Adjusted RNFL thickness was 128.1 ± 1.32 µm in the superior region, 130.7 ± 1.32 µm in the inferior region, 72.7 ± 1.32 µm in the temporal region, and 75.1 ± 1.32 µm in the nasal region. Relative to the superior region, RNFL thickness did not differ significantly in the inferior region (B = 2.60, 95% CI = −0.41 to 5.60, p = 0.091), whereas it was significantly lower in the temporal (B = −55.47, 95% CI = −58.47 to

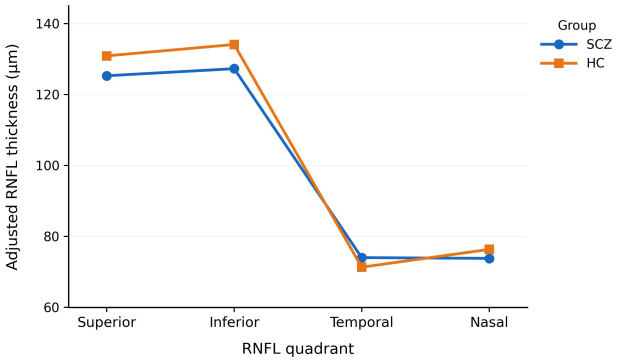


Fig. 2. Adjusted estimated marginal RNFL thicknesses across superior, inferior, temporal, and nasal regions in patients with schizophrenia and healthy controls. Points represent adjusted estimated marginal means obtained from a linear mixed-effects model with a participant-specific random intercept, adjusted for age and years of education. Error bars indicate standard errors. Each group included 65 participants.

Table 2. Linear mixed-effects model results and adjusted estimated marginal means for GCC thickness.

A. Fixed-effect estimates and contrasts

Effect/contrast	B	SE	95% CI	F	*p*
Group	—	—	—	7.7	**0.006**
HC − SCZ	4.67	1.68	1.37–7.96	—	**0.006**
Eye	—	—	—	0.35	0.557
Left − Right	0.30	0.51	−0.70–1.30	—	0.557
GCC sector	—	—	—	16.80	**<0.001**
Inferior − Superior	2.09	0.51	1.09–3.09	—	**<0.001**
Age	0.02	0.12	−0.20–0.25	0.04	0.850
Years of education	0.50	0.26	−0.01–1.01	3.69	0.057
Group × Eye	0.89	1.02	−1.11–2.89	0.76	0.383
Group × GCC sector	−0.97	1.02	−2.97–1.03	0.90	0.343
Eye × GCC sector	1.85	1.02	−0.15–3.85	3.27	0.071
Group × Eye × GCC sector	1.38	2.04	−2.62–5.39	0.46	0.498

B. Adjusted estimated marginal means

Variable	Category	Estimated mean ± SE, µm	95% CI, µm
Group	Patients with SCZ	96.70 ± 1.09	94.6–98.9
	HC	101.40 ± 1.09	99.2–103.5
Eye	Right	98.90 ± 0.75	97.4–100.4
	Left	99.20 ± 0.75	97.7–101.0
GCC sector	Superior	98.00 ± 0.75	96.5–99.5
	Inferior	100.10 ± 0.75	98.6–101.6

Note: A linear mixed-effects model with a participant-specific random intercept was used to account for repeated measurements obtained from both eyes and GCC sectors within the same participant. Group, eye, GCC sector, and their interaction terms were entered as fixed effects. Age and years of education were included as covariates. Model parameters were estimated using restricted maximum likelihood (REML) with degrees of freedom approximated using the Satterthwaite method. B values represent unstandardized fixed-effect coefficients. The participant-level random-intercept variance was 55.4 (SD = 7.44), and the residual variance was 33.9 (SD = 5.82). The model had an intraclass correlation coefficient of 0.62 and a conditional R^2 of 0.661. Statistically significant *p* values are shown in bold. Abbreviations: B, unstandardized fixed-effect coefficient; CI, confidence interval; GCC, ganglion cell complex; ICC, intraclass correlation coefficient; REML, restricted maximum likelihood; SE, standard error.

−52.46, $p < 0.001$) and nasal regions (B = −53.02, 95% CI = −56.02 to −50.01, $p < 0.001$). Neither age (F = 0.48, $p = 0.488$) nor years of education (F = 0.25, $p = 0.621$) was significantly associated with RNFL thickness.

The group × RNFL measurement interaction was statistically significant (F = 3.83, $p = 0.010$). However, after Holm correction for multiple comparisons, none of the region-specific group differences reached statistical significance. The group difference was greatest in the inferior region (B = 6.82, 95% CI = 1.07 to 12.57, Holm-adjusted $p = 0.080$), followed by the superior (B = 5.60, 95% CI = −0.15 to 11.35, Holm-adjusted $p = 0.168$), temporal (B = −2.69, 95% CI = −8.44 to 3.06, Holm-adjusted $p = 0.716$), and nasal regions (B = 2.53, 95% CI = −3.22 to 8.29, Holm-adjusted $p = 0.716$).

The eye × RNFL measurement interaction was also statistically significant (F = 3.36, $p = 0.018$). However, after Holm correction for multiple comparisons, none of the region-specific differences between the left and right eyes reached statistical significance. The corresponding Holm-adjusted *p* values were 0.156 for the superior region (B = 4.48, 95% CI = 0.23 to 8.74), 0.512 for the inferior region (B = 2.09, 95% CI = −2.16 to 6.35), 0.512 for the temporal region (B = −2.46, 95% CI = −6.72 to 1.79), and 0.177 for the nasal region (B = −4.10, 95% CI = −8.35 to 0.15). The group × eye interaction (F = 1.80, $p = 0.180$) and the group × eye × RNFL measurement interaction (F = 0.30, $p = 0.823$) were not statistically significant.

The participant-level random-intercept variance was 75.4, the residual variance was 305.2, the intraclass correlation coefficient was 0.198, and the conditional R^2 was 0.738.

3.4 Relationships Between OCT Parameters and Psychometric Measures

Spearman's rank correlations between OCT parameters and psychometric scale scores in patients with SCZ are

Table 3. Linear mixed-effects model results and adjusted estimated marginal means for RNFL thickness.

A. Fixed-effect estimates and contrasts

Effect/contrast	B	SE	95% CI	F	*p*
Group	—	—	—	1.87	0.174
HC − SCZ	3.07	2.24	−1.33–7.46	—	0.174
Eye	—	—	—	0.00	0.997
Left − Right	0.00	1.08	−2.12–2.13	—	0.997
RNFL measurement	—	—	—	877.60	**<0.001**
Inferior − Superior	2.60	1.53	−0.41–5.60	—	0.091
Temporal − Superior	−55.47	1.53	−58.47 to −52.46	—	**<0.001**
Nasal − Superior	−53.02	1.53	−56.02 to −50.01	—	**<0.001**
Age	−0.11	0.15	−0.41–0.19	0.48	0.488
Years of education	0.17	0.35	−0.51–0.85	0.25	0.621
Group × Eye	—	—	—	1.80	0.180
Group × RNFL measurement	—	—	—	3.83	**0.010**
Superior: HC − SCZ	5.60	2.92	−0.15–11.35	3.66	0.168[a]
Inferior: HC − SCZ	6.82	2.92	1.07–12.57	5.44	0.080[a]
Temporal: HC − SCZ	−2.69	2.92	−8.44–3.06	0.85	0.716[a]
Nasal: HC − SCZ	2.53	2.92	−3.22–8.29	0.75	0.716[a]
Eye × RNFL measurement	—	—	—	3.36	**0.018**
Superior: Left − Right	4.48	2.17	0.23–8.74	4.28	0.156[a]
Inferior: Left − Right	2.09	2.17	−2.16–6.35	0.93	0.512[a]
Temporal: Left − Right	−2.46	2.17	−6.72–1.79	1.29	0.512[a]
Nasal: Left − Right	−4.10	2.17	−8.35–0.15	3.58	0.177[a]
Group × Eye × RNFL measurement	—	—	—	0.30	0.823

B. Adjusted estimated marginal means

Variable	Category	Estimated mean ± SE, µm	95% CI, µm
Group	HC	103.00 ± 1.46	100.3–106.0
	SCZ	100.00 ± 1.46	97.2–103.0
Eye	Right	102.00 ± 1.08	99.5–104.0
	Left	102.00 ± 1.08	99.5–104.0
RNFL measurement	Superior	128.10 ± 1.32	125.5–130.7
	Inferior	130.70 ± 1.32	128.1–133.3
	Temporal	72.70 ± 1.32	70.1–75.3
	Nasal	75.10 ± 1.32	72.5–77.7

Note: A linear mixed-effects model with a participant-specific random intercept was used to account for repeated measurements obtained from both eyes and multiple RNFL measurements within the same participant. Group, eye, RNFL measurement, and their interaction terms were entered as fixed effects. Age and years of education were included as covariates. Model parameters were estimated using restricted maximum likelihood (REML) with degrees of freedom approximated using the Satterthwaite method. B values represent unstandardized fixed-effect coefficients. The participant-level random-intercept variance was 75.4 (SD = 8.68), and the residual variance was 305.2 (SD = 17.47). The model had an intraclass correlation coefficient (ICC) of 0.198 and a conditional R^2 of 0.738. Statistically significant *p* values are shown in bold. Abbreviations: RNFL, retinal nerve fiber layer. [a]*p* values for simple-effects comparisons were adjusted for multiple comparisons using the Holm method. The reported 95% confidence intervals for these comparisons are unadjusted.

presented in Table 4. No statistically significant correlations were observed between GCC or RNFL thickness and PANSS positive, negative, general psychopathology, or total scores, FRSS total score, or WHODAS 2.0 total score (ρ range, −0.235 to 0.230; all $p > 0.05$).

3.5 Factors Associated with Functional Recovery and Disability

The results of the bootstrap multiple linear regression analyses for FRSS and WHODAS 2.0 total scores are presented in Table 5. The model for FRSS total score was statistically significant ($R^2 = 0.404$, adjusted $R^2 = 0.306$, F (9,

Table 4. Spearman rank correlations between OCT parameters and psychometric scale scores in patients with schizophrenia (n = 65).

OCT parameter	Mean ± SD, µm	PANSS-P	PANSS-N	PANSS-GP	PANSS-T	FRSS	WHODAS 2.0
Mean superior GCC thickness	95.54 ± 9.63	−0.190	−0.111	−0.172	−0.162	0.110	−0.088
Mean inferior GCC thickness	97.15 ± 10.40	−0.235	−0.105	−0.133	−0.150	−0.007	−0.062
Mean superior RNFL thickness	124.78 ± 18.48	0.165	0.041	0.085	0.080	−0.038	−0.018
Mean inferior RNFL thickness	126.76 ± 20.45	−0.060	0.012	0.028	−0.006	−0.093	−0.008
Mean temporal RNFL thickness	73.45 ± 13.88	−0.040	0.084	0.124	0.075	0.078	0.230
Mean nasal RNFL thickness	73.29 ± 14.57	0.075	0.014	−0.021	−0.002	−0.044	0.031

Note: Values are presented as Spearman rank correlation coefficients (ρ). All tests were two-sided. None of the correlations between OCT parameters and psychometric scale scores reached statistical significance (all $p > 0.05$). Abbreviations: FRSS, Functional Recovery Scale in Schizophrenia; OCT, optical coherence tomography; PANSS, Positive and Negative Syndrome Scale; PANSS-GP, PANSS general psychopathology subscale; PANSS-N, PANSS negative syndrome subscale; PANSS-P, PANSS positive syndrome subscale; PANSS-T, PANSS total score; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0.

55) = 4.139, $p < 0.001$). After adjustment for age, duration of illness, and regional GCC and RNFL thicknesses, higher PANSS total scores were independently associated with lower FRSS total scores (B = −0.273, bootstrap 95% CI = −0.357 to −0.172, $p < 0.001$). Age, duration of illness, mean superior and inferior GCC thicknesses, and mean superior, inferior, temporal, and nasal RNFL thicknesses were not independently associated with FRSS total score (all $p > 0.05$).

The model for WHODAS 2.0 total score was also statistically significant ($R^2 = 0.356$, adjusted $R^2 = 0.251$, F(9, 55) = 3.379, $p = 0.002$). After adjustment for age, duration of illness, and regional GCC and RNFL thicknesses, higher PANSS total scores were independently associated with higher WHODAS 2.0 total scores (B = 0.222, bootstrap 95% CI = 0.097 to 0.357, $p = 0.001$). Age, duration of illness, mean superior and inferior GCC thicknesses, and mean superior, inferior, temporal, and nasal RNFL thicknesses were not independently associated with WHODAS 2.0 total score (all $p > 0.05$). All VIF values were below 5, indicating no evidence of severe multicollinearity.

4. Discussion

In this study, retinal structural parameters assessed by OCT were compared between patients with SCZ aged 40 years or younger who were clinically stable and HC. Their associations with functional recovery, disability, and psychopathology severity were also examined. The main finding was that GCC thickness was significantly lower in patients with SCZ than in HC after adjustment for age and years of education, whereas the overall group effect for RNFL thickness was not significant. Although the group × RNFL region interaction was significant, none of the region-specific group comparisons remained significant after Holm correction for multiple comparisons. In the multiple regression analyses, however, retinal structural parameters were not independently associated with functional recovery or disability, whereas PANSS total score was independently associated with both outcomes. These findings suggest that retinal thinning may represent a neurobiological feature associated with SCZ but may have limited value in explaining individual differences in functioning and disability. Although OCT measurements may be useful for identifying group-level retinal structural differences in schizophrenia, they should be interpreted alongside broader biopsychosocial factors when evaluating clinical and functional outcomes.

In a meta-analysis by Pan et al. [20], mean RNFL thickness was significantly lower in patients with SCZ than in HC, with more pronounced thinning in the inferior, nasal, and temporal quadrants. Subsequent meta-analyses have reported thinning not only of the peripapillary RNFL but also of the macular ganglion cell-inner plexiform layer and other macular structures in schizophrenia-spectrum disorders [14,21]. In the present study, the finding of lower GCC thickness in the schizophrenia group is consistent with the literature. In contrast, no significant overall group effect was found for RNFL thickness; despite a significant Group × RNFL Region interaction, no significant differences between groups were detected in any quadrant after Holm correction. Miller et al. (2020) [22] did not find a significant difference in RNFL thickness between patients with schizophrenia spectrum disorders and healthy controls but reported a reduction in macular volume in the

Table 5. Bootstrap multiple linear regression analyses of variables associated with functional recovery and disability in patients with schizophrenia (n = 65).

Model 1. Dependent variable: FRSS total score					
Independent variable	**B**	**SE**	***p***	**Bootstrap 95% CI**	**VIF**
Age	0.043	0.352	0.934	−0.650–0.769	1.59
Duration of illness	0.207	0.402	0.614	−0.550–1.009	1.87
PANSS total score	−0.273	0.047	**<0.001**	−0.357 to −0.172	1.28
Mean superior GCC thickness	0.143	0.352	0.794	−0.610–0.761	2.35
Mean inferior GCC thickness	−0.146	0.390	0.812	−0.903–0.653	3.16
Mean superior RNFL thickness	0.159	0.149	0.300	−0.126–0.455	2.52
Mean inferior RNFL thickness	−0.188	0.142	0.153	−0.498–0.066	2.71
Mean temporal RNFL thickness	0.226	0.162	0.193	−0.124–0.523	1.26
Mean nasal RNFL thickness	0.044	0.152	0.629	−0.242–0.351	1.40
Model fit	$R^2 = 0.404$; $F(9,55) = 4.139$; $p < 0.001$				
Model 2. Dependent variable: WHODAS 2.0 total score					
Independent variable	**B**	**SE**	***p***	**Bootstrap 95% CI**	**VIF**
Age	0.016	0.350	0.880	−0.574–0.829	1.59
Duration of illness	0.224	0.424	0.603	−0.681–0.987	1.87
PANSS total score	0.222	0.066	**0.001**	0.097–0.357	1.28
Mean superior GCC thickness	−0.147	0.324	0.685	−0.808–0.454	2.35
Mean inferior GCC thickness	0.004	0.385	0.934	−0.661–0.868	3.16
Mean superior RNFL thickness	0.013	0.186	0.790	−0.318–0.416	2.52
Mean inferior RNFL thickness	−0.073	0.165	0.690	−0.386–0.259	2.71
Mean temporal RNFL thickness	0.321	0.183	0.081	−0.042–0.688	1.26
Mean nasal RNFL thickness	0.007	0.194	0.991	−0.411–0.365	1.40
Model fit:	$R^2 = 0.356$; $F(9,55) = 3.379$; $p = 0.002$				

Note: Age, duration of illness, PANSS total score, mean superior and inferior GCC thicknesses, and mean superior, inferior, temporal, and nasal RNFL thicknesses were entered simultaneously into both regression models. Regional GCC and RNFL thicknesses represent the mean of the corresponding measurements from the right and left eyes. Unstandardized regression coefficients (B), standard errors (SE), *p* values, and bias-corrected and accelerated (BCa) 95% confidence intervals were obtained from the bootstrap analysis based on 5000 resamples. Multicollinearity was assessed using the variance inflation factor (VIF); all VIF values were below 5. All statistical tests were two-sided, and statistically significant *p* values are shown in bold. Abbreviations: VIF, variance inflation factor.

patient group. In a more recent review, Blose and Silverstein (2026) [23] noted that findings regarding peripapillary RNFL thinning were inconsistent across studies; in contrast, macular thinning—which largely reflects changes in the ganglion cell layer and inner plexiform layer—was reported more consistently. In line with this, the finding in our study that GCC thickness was significantly lower, even though the overall RNFL group effect was not significant, is consistent with the literature indicating that different retinal structures are affected to varying degrees.

Whereas the GCC reflects retinal structures containing the cell bodies, dendritic processes, and synaptic connections of retinal ganglion cells, the RNFL is composed predominantly of unmyelinated ganglion cell axons that form the optic nerve [24,25]. In this study, GCC thickness was found to be significantly lower in the SCZ group, whereas the overall group effect for RNFL was not significant. This pattern suggests that changes in macular ganglion cell structures may be more pronounced than peripapillary axonal changes in the current sample. Previous studies have suggested that ganglion cell and inner plexiform layer measurements may be more closely associated with illness severity than RNFL thickness [26]. However, since the GCC is a composite measure, the current data do not allow us to determine which sublayer the observed difference originates from. Furthermore, despite a significant Group × Region interaction for RNFL, the absence of any significant group differences in any quadrant following Holm's correction precludes a definitive conclusion regarding axonal involvement specific to a particular region.

It remains unclear whether retinal alterations in SCZ reflect an underlying neurodevelopmental vulnerability,

illness-related progression, or a combination of these mechanisms [23]. Komatsu et al. [14] suggested that retinal alterations in schizophrenia-spectrum disorders may serve as both trait and state markers. Reduced inner plexiform layer thickness in unaffected first-degree relatives compared with HC supports the possibility of a familial or neurodevelopmental vulnerability preceding illness onset [27]. However, meta-regression findings linking retinal thinning to illness duration and the severity of both positive and negative symptoms suggest that retinal alterations may also reflect illness-related or progressive processes [14]. Similarly, individual studies have reported associations between illness duration and reductions in RNFL and macular thickness [28]. Longitudinal studies with repeated OCT assessments beginning at the first episode are needed to clarify these possibilities.

A significant Group × Region interaction was found for RNFL thickness ($F = 3.83$, $p = 0.010$). However, following Holm correction, no significant differences were detected between groups in any of the superior, inferior, temporal, or nasal quadrants. Therefore, while the interaction indicates regional variability in the RNFL, it should not be interpreted as evidence of group differences specific to a particular quadrant. Furthermore, the lack of a significant overall group effect does not support the interpretation that there is widespread RNFL thinning in the SCZ group. Group × Eye and Group × Region interactions for GCC were not found to be significant, indicating that the difference in GCC between groups did not vary significantly across eyes or superior–inferior regions. The non-significant main effect of Eye and Group × Eye interaction for GCC and RNFL thickness suggests the absence of robust overall or schizophrenia-specific retinal lateralization. Although the Eye × RNFL Region interaction was significant, none of the region-specific right–left eye differences remained significant after Holm correction. Since contrast sensitivity impairment has been consistently reported in schizophrenia, structural retinal findings should be evaluated together with functional visual alterations [29]. A recent preliminary study reported abnormal low-spatial-frequency contrast sensitivity in individuals with early cannabis exposure and proposed combining functional visual testing with OCT to investigate potential retinal biomarkers relevant to schizophrenia risk [30]. However, contrast sensitivity was not assessed in the present study, and the sample size may have limited our ability to detect smaller disease-specific laterality effects.

One of the secondary aims of the present study was to examine whether the retinal structural alterations observed in the SCZ group were associated with functional recovery and disability. However, no significant associations were observed between GCC or RNFL thickness and either functional outcome. Similarly, in multiple regression analyses adjusted for age, illness duration, and psychopathology severity, GCC and RNFL thicknesses were not independently associated with FRSS or WHODAS 2.0 scores. These findings indicate that no independent contribution of the OCT parameters examined to individual differences in functional recovery and disability was detected in the current sample; however, they do not rule out the possibility of smaller associations.

Several factors may explain the absence of significant associations between retinal thickness and functional outcomes. First, functional recovery is a multidimensional outcome that is not determined by a single biological system. In addition to psychopathology, daily functioning is shaped by the interplay of neurocognition, social cognition, motivation, personal resources, physical health, social support, access to treatment and rehabilitation, and broader social and environmental conditions [6,31,32]. Although retinal layer thickness may reflect a specific biological dimension related to the central nervous system, it may not be directly or strongly associated with real-world functioning.

Previous studies examining associations among retinal measurements, cognitive performance, and visual processing in SCZ have yielded inconsistent findings [33,34]. Giordano et al. [35] reported that associations between neurocognitive impairment and functional outcomes may be partly or fully accounted for by negative symptoms and social cognition. Because neurocognition and social cognition were not assessed, the present study could not examine their potential contribution to the relationships between retinal measurements and functional outcomes. Given the close relationship of cognitive functioning with both functional recovery and disability, the absence of these assessments limits the interpretation of the non-significant associations between OCT parameters and FRSS or WHODAS 2.0 scores. Therefore, these findings should not be interpreted as evidence that retinal parameters are unrelated to functional outcomes. Future studies incorporating OCT measurements together with neurocognitive and social cognitive assessments are needed to clarify these relationships.

The present retinal findings may also be considered within the broader retina-LGN-visual cortex pathway. Glaucoma has been described as a model of transsynaptic neural degeneration involving interconnected visual structures in the eye and brain [36]. In schizophrenia, postmortem studies have not identified significant alterations in LGN volume or neuron number [37], whereas an MRI study reported LGN volume alterations in specific clinical subgroups [38]. Recent reviews also indicate that the contribution of precortical visual structures, including the retina and LGN, remains unresolved [39]. These findings raise the possibility that retinal alterations in schizophrenia may reflect disturbances distributed across the visual pathway rather than an exclusively retinal process. Nevertheless, because the present study did not include neuroimaging of the LGN or visual cortex, it cannot determine whether the observed GCC thinning is related to central visual-pathway abnormalities or transsynaptic processes.

The cross-sectional design of the present study did not allow us to determine the temporal relationship between GCC thinning and illness onset or course. Therefore, we cannot establish whether reduced GCC thickness represents a premorbid neurodevelopmental trait, a progressive illness-related alteration, or a combination of these processes. Another possibility is that retinal measurements may reflect a relatively stable biological trait related to illness susceptibility or cumulative illness burden rather than current functional status [14]. Although the absence of a significant association between GCC and RNFL measurements and current PANSS scores is consistent with this interpretation, it does not, on its own, demonstrate that retinal measurements are a trait indicator. Longitudinal studies incorporating repeated OCT measurements alongside concurrent assessments of symptom severity and functioning are needed to determine whether retinal measurements serve primarily as trait or state markers in SCZ. Furthermore, the current sample size may not be sufficient to detect small associations between retinal parameters and clinical and functional outcomes; therefore, associations that were not found to be statistically significant do not rule out the existence of smaller true effects.

In the present study, greater psychopathology severity was associated with poorer functional recovery and greater disability. In regression analyses controlling for age, duration of illness, GCC, and RNFL measurements, only the PANSS total score remained independently associated with both functional outcomes, highlighting the close relationship between overall psychopathology severity and functioning. These findings are consistent with previous studies demonstrating associations between psychopathology severity and functional outcomes in SCZ [32,40]. Furthermore, FRSS and WHODAS 2.0 scores were moderately and inversely correlated, indicating that better functional recovery was associated with lower disability. This finding is consistent with previous studies showing an inverse association between functional recovery and disability in patients with SCZ [41,42].

The present study had several methodological strengths. Excluding participants with ocular or major systemic conditions that could affect OCT measurements reduced potential confounding and improved the reliability of the retinal assessments. Furthermore, measurements obtained from both eyes and multiple retinal regions were analyzed using linear mixed-effects models, thereby accounting for the within-participant dependence of repeated observations. Separate models were fitted for GCC and RNFL thickness, and age and years of education were included as covariates, strengthening the validity of the between-group comparisons.

Limitations

The present study also had several limitations. First, its cross-sectional design precluded conclusions regarding whether the observed retinal alterations preceded illness onset, developed during the course of the illness, or progressed over time. Second, the modest sample size may have limited the detection of small associations. The substantial differences between the groups in age and years of education should be considered when interpreting the findings. Although both variables were included as covariates in the between-group analyses, statistical adjustment may not have fully eliminated residual confounding. This is particularly relevant for age because retinal thickness may change with aging, whereas differences in education may reflect broader developmental and socioeconomic differences between the groups. Therefore, the findings should be interpreted cautiously and confirmed in more closely matched samples. Furthermore, the single-center setting and inclusion of relatively young, clinically stable patients may limit the generalizability of the findings to older individuals and patients at different stages of illness.

In addition, healthy controls were recruited from individuals attending the Ophthalmology Outpatient Clinic for routine eye examinations rather than from the general population. Although this approach ensured that both groups underwent the same standardized ophthalmological examination and OCT acquisition protocol, it may have introduced selection bias and limited the representativeness of the control sample.

Detailed information on antipsychotic type, dose, treatment duration, and chlorpromazine-equivalent dose were not collected. Therefore, the potential direct effects of antipsychotic exposure and its indirect effects through metabolic or vascular pathways could not be examined, and residual confounding related to treatment cannot be excluded.

Our a priori power analysis was designed for the primary between-group comparisons and may not have provided sufficient power to detect small or modest associations in the secondary correlation and regression analyses. Therefore, the non-significant associations between OCT parameters and psychometric measures should not be interpreted as definitive evidence of no relationship and do not exclude smaller effects that might be detected in larger samples.

Detailed information on potential retinal confounders, including antipsychotic type, dose, and treatment duration; cumulative smoking exposure; body mass index; and metabolic characteristics, was not available. Ophthalmological variables such as axial length and retinal microvascular structure were also not assessed, which may have limited the interpretation of the OCT findings. Finally, the absence of neurocognitive, social cognitive, and performance-based functional capacity measurements precluded the examination of potential indirect pathways linking retinal alterations to functional outcomes.

5. Conclusions

In conclusion, the present study demonstrated that, after adjustment for age and years of education, GCC thickness was significantly lower in clinically stable patients with SCZ than in HC, whereas the overall group effect for RNFL thickness was not significant. Although the group × RNFL region interaction was significant, none of the region-specific group comparisons remained significant after Holm correction for multiple comparisons. These findings support the potential utility of OCT as a noninvasive and reproducible research tool for detecting group-level retinal structural alterations in SCZ. No statistically significant associations between retinal structural parameters and psychopathology severity, functional recovery, or disability were detected in the present sample. These findings do not support retinal thickness as an independent correlate of functional outcomes in this sample; however, small or modest associations cannot be excluded. In contrast, higher PANSS total scores were independently associated with poorer functional recovery and greater disability.

These results suggest that retinal thinning may represent a neurobiological feature associated with SCZ but has limited value as a stand-alone indicator of individual functional outcomes. Longitudinal, multicenter studies with larger and better-matched samples are needed to clarify the potential value of OCT-derived retinal measurements as candidate biomarkers. Future multimodal studies combining OCT with structural and functional neuroimaging of the LGN and visual cortex may clarify the direction and clinical significance of the relationship between retinal alterations and central visual-pathway abnormalities in schizophrenia. Future studies combining laterality-focused OCT analyses with functional visual assessments, particularly contrast sensitivity, may help clarify the clinical significance of retinal asymmetry in schizophrenia. Future interdisciplinary studies integrating OCT-derived retinal measurements with computational approaches, including deep learning and multimodal data fusion, as well as neurophysiological, neurocognitive, and genetic measures, may enable a more comprehensive evaluation of the potential diagnostic and prognostic value of retinal biomarkers in schizophrenia.

Abbreviations

SCZ, schizophrenia; HC, healthy controls; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex; PANSS, Positive and Negative Syndrome Scale; PANSS-P, PANSS positive syndrome subscale; PANSS-N, PANSS negative syndrome subscale; PANSS-GP, PANSS general psychopathology subscale; PANSS-T, PANSS total score; FRSS, Functional Recovery Scale in Schizophrenia; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SD-OCT, spectral-domain optical coherence tomography; SSI, signal strength index; REML, restricted maximum likelihood; ICC, intraclass correlation coefficient; CI, confidence interval; SE, standard error; B, unstandardized regression coefficient; VIF, variance inflation factor; BCa, bias-corrected and accelerated; R^2, coefficient of determination; FROGS, Functional Remission of General Schizophrenia Scale; SD, standard deviation.

Availability of Data and Materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

MZ and KU designed the research study. MZ and NAK performed the clinical and ophthalmological assessments and acquired the data. FK and KU analyzed the data, and TS, KU and KO interpreted the data. MZ and KO wrote the initial draft of the manuscript. TS and KU supervised the manuscript preparation and critically reviewed the manuscript for important intellectual content. NAK and FK critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Malatya Turgut Özal University Health Sciences Scientific Research Ethics Committee (Decision No. 2025/254, dated July 30, 2025). Written informed consent was obtained from all participants prior to enrollment.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used ChatGPT (GPT-5.6; OpenAI, San Francisco, CA, USA) solely to improve the English language, gram-

matical accuracy, readability, and clarity of the text. The authors subsequently reviewed and edited all AI-assisted content and take full responsibility for the accuracy, integrity, and scientific content of the final manuscript. Generative AI was not used to generate or analyze data, perform statistical analyses, interpret the study findings, or formulate the scientific conclusions.

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