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Retinal structure and its relationship with premorbid, clinical, and cognitive variables in young Spanish patients with early course schizophrenia spectrum disorders

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ABSTRACT

Emerging evidence suggests that retinal structural alterations are present in schizophrenia spectrum disorders (SSD), potentially reflecting broader neurodevelopmental and neurodegenerative processes. This cross-sectional study investigates retinal thickness and its clinical correlations in a sample of early-course SSD patients compared to healthy controls (HCs). One hundred-two eyes from 26 SSD cases and 25 age- and sex-matched HCs were included. Retinal structure was evaluated using Spectral-Domain Optical Coherence Tomography (SD-OCT), focusing on the peripapillary retinal nerve fiber layer (pRNFL), macular volume/thickness, and ganglion cell-inner plexiform layer (GCL+IPL) thickness. Although SSD cases showed increased peripapillary retinal nerve fiber layer (pRNFL) thickness in specific quadrants, most retinal parameters did not differ significantly between groups. Preliminary associations were observed between retinal measures, premorbid adjustment, DUP, and cognitive performance. These findings, while suggesting the potential of retinal imaging as a tool for early detection and monitoring of psychotic disorders, must be interpreted with caution. Further longitudinal and multimodal research is warranted to explore the association between these retinal changes and neuro-inflammation, neurodegeneration, and overall brain health in SSD patients.

1. Introduction

Schizophrenia spectrum disorders (SSD), including schizophrenia, schizoaffective disorder, and brief psychotic disorder, share a psychopathological basis characterized by typical psychotic symptoms during specific periods (American Psychiatric Association, 2013; Gama Marques and Ouakinin, 2021; Schönfeldt-Lecuona et al., 2020; Jauhar et al., 2022). While the pathophysiology of SSD is not yet fully understood, emerging research has identified the retina as a promising biomarker for brain health, given its direct connection to the central nervous system

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(Silverstein et al., 2020). Advances in imaging technologies, particularly Optical Coherence Tomography (OCT), have enabled the detailed in vivo examination of retinal structure, offering a unique opportunity to explore their potential role in monitoring the disease progression and cognitive decline associated with SSD (Silverstein et al., 2022; Silverstein and Rosen, 2015).

Previous studies have demonstrated that patients with SSD exhibit structural changes in the retina, including the peripapillary retinal nerve fiber layer (pRNFL), the macula and the ganglion cell layer (GCL) (Gonzalez-Diaz et al., 2022; Kazakos and Karageorgiou, 2020; Kennedy et al., 2023; Komatsu et al., 2023, 2022; Lizano et al., 2020; Pan et al., 2018; Prasannakumar et al., 2023). Prior research has also reported retinal changes in multiple neuropsychiatric disorders (Alves et al., 2023; Davis et al., 2024; Mirmosayyeb et al., 2023; Rifai et al., 2021; Shi et al., 2024). Recent literature suggests that these retinal changes are related to clinical severity (Ascaso et al., 2015; Celik et al., 2016; Gandu et al., 2021; Sarkar et al., 2021; Topcu-Yilmaz et al., 2019) and could reflect the neurodegenerative, neuroinflammatory, and metabolic processes underlying SSD (Silverstein, 2020; Silverstein et al., 2021; Vujosevic et al., 2023). Despite these advances, significant gaps remain in the literature. Notably, the relationships between retinal measures and the duration of untreated psychosis or the premorbid adjustment—key factors influencing the course of SSD—have not been previously explored. Understanding how early-life social and academic functioning, commonly referred to as premorbid adjustment, relates to retinal abnormalities could provide valuable insights into the neurodevelopmental aspects of SSD. Premorbid adjustment refers to the level of social, academic, and general functioning before the onset of a mental disorder (Punsoda-Puche et al., 2024).

Additionally, there is a growing interest in the association between retinal measures and cognitive performance. However, the heterogeneity in study designs, populations, and cognitive assessments has led to mixed results, with some studies reporting significant associations between retinal thinning and cognitive impairment while others do not (Gonzalez-Diaz et al., 2022; Kurtulmus et al., 2023; Liu et al., 2021, 2020; Padmanabhan et al., 2024; Sakalli Kani et al., 2023). This lack of clarity underscores the need for further research to elucidate the specific retinal biomarkers that might correlate with various aspects of cognitive functioning in SSD. Therefore, this study aims to address these critical gaps by exploring the relationship between retinal structure and clinical, course-related, functional, premorbid, and cognitive variables in a set of SSD patients compared to healthy controls (HCs).

2. Methods

2.1. Participants

This cross-sectional study included a sample of patients diagnosed with schizophrenia or schizoaffective disorder according to DSM-5 criteria with <5 years since diagnosis and a sex- and age-matched (±2 years) group of HCs aged between 18 and 40 years old. The study received approval from the Institutional Review Board (IRB) of Hospital Clínic de Barcelona (protocol HCB/2022/0227), and all participants provided informed consent before participating. Patients in the SSD group were recruited consecutively from clinical settings, while HCs were recruited from the community. The SSD group comprised individuals with a clinical diagnosis of schizophrenia or schizoaffective disorder according to DSM-5 criteria.

Exclusion criteria for both groups included the presence of neurological diseases, severe ocular or head trauma, alcohol/substance abuse, high blood pressure, diabetes, ocular surgery, current pregnancy or breastfeeding, and any pre-existing ophthalmological conditions that could affect retinal measurements, such as refraction errors >±6 diopters macular degeneration, amblyopia, media opacities (i.e., cataracts), or glaucoma. Height and weight were measured for all participants, and Body Mass Index (BMI) was computed as kg/m^2. Blood pressure (BP) was measured using a calibrated sphygmomanometer, and mean BP was calculated according to standard methods (Yospon and Rojananuangnit, 2023). For SSD patients, information regarding current and past substance use patterns and psychopharmacological treatment was collected, and the antipsychotic dose was computed in Risperidone equivalent doses according to Leucht et al. (Leucht et al., 2015, 2014). Duration of Untreated Psychosis (DUP) was calculated as the time elapsed between the onset of the first clear psychotic symptom (hallucinations, delusions, or disorganized thought or behavior) and the date of diagnosis. The time since diagnosis was calculated as the time elapsed between the date of diagnosis and the date of the ophthalmologic evaluation.

2.2. Assessment instruments

An ad-hoc form was used to collect sociodemographic data. Socioeconomic status was assessed with the Hollingshead-Redlich scale (Ritsher et al., 2001), while treatment adherence was assessed with the Morinsky-Green Adherence Scale (Morisky et al., 1986). To assess premorbid adjustment, the Spanish version of the Cannon-Spoor's Premorbid Adjustment Scale (PAS) was administered (Cannon-Spoor et al., 1982). This scale evaluates social and academic functioning before the onset of psychosis, covering four age ranges: childhood(<12 years), early adolescence(12–15 years), late adolescence(16–18 years), and adulthood(>18 years). For this study, the childhood and adolescence subscales were used. Current functioning was measured with the Global Assessment of Functioning (GAF) scale (Association, 1994), while symptom severity was evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Except for the GAF, higher scores in the rest of the scales represent worst premorbid adjustment, symptom severity, and disability.

A comprehensive neuropsychological battery test was administered to assess cognitive performance, including:

- Verbal memory, assessed with the California Verbal Learning Test (CVLT), which included the total List A, immediate free and cued recall, and delayed free and cued recall (Delis et al., 2000).
- Processing Speed, assessed with the Trail Making Test Form A (TMT-A) (Reitan and Wolfson, 1995).
- Verbal Working Memory, assessed with the Letter-number sequencing Subtest of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997).
- Sustained attention, assessed using the Conners' Continuous Performance Test (CPT), which included the measurement of commission errors, reaction time, and the d' attentiveness variable (Conners, 2004).
- Executive function, assessed using the Wisconsin Card Sorting Test (WCST), which included the number of categories achieved, total errors, and perseverative errors (Heaton, 2008).
- Emotional intelligence was assessed with the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (Mayer et al., 2003).

All neurocognitive measures were transformed into T-scores; in most cases, higher scores correspond to better performance, except for the CPT test. A principal component analysis (PCA) was conducted to reduce the dimensionality of the neurocognitive variables and identify underlying components that explain the variance in the data. The analysis was performed using a correlation matrix with Varimax rotation and included the neurocognitive tests performed for verbal memory, sustained attention, and executive function (Supplementary Table S1). The Kaiser-Meyer-Olkin measure (KMO=0.664) confirmed the sampling adequacy, and Bartlett's test of sphericity was significant (χ^2=143.319,$p < 0.001$), indicating that the data were appropriate for conducting a PCA. The PCA revealed three distinct components explaining 85.05% of the variance. The first component, "Verbal Memory," explained 40.83% of the variance and showed high loadings on variables related to verbal

memory tasks assessed through the CVLT, including total List A, immediate free recall, immediate cued recall, delayed free recall, and delayed cued recall. The second component, "Executive Function," accounted for 20.36% of the variance and was primarily defined by executive function variables measured by the WCST, including the number of categories achieved, total errors, and perseverative errors. The third component, "Sustained Attention," explained an additional 23.86% of the variance, associated with sustained attention tasks assessed through the CPT, including commission errors, reaction time, and the d' attentiveness variable.

2.3. Ophthalmic evaluation and oct

All participants underwent a comprehensive ophthalmological examination, including visual acuity testing using the Snellen Eye Chart. Retinal OCT scans were performed with a Spectralis SD-OCT device (Heyex 5.30 Heidelberg Engineering, Germany) under dim lighting conditions and using the eye-tracking modality without pupillary dilation. The pRNFL thickness was measured using a ring-type scan (12-circle diameter) centered around the optic nerve head, with automatic centering and manual correction (100 ART;1536 A-Scans per B scan). The macular scan protocol involved a 20 × 20° horizontal raster scan centered on the fovea, consisting of 25 B-scans (ART≥9;512 A-scans per B-scan). An experienced optometrist (SAA) segmented the intraretinal layers to quantify macular GCL+IPL thickness using the standard 6.0c version of the Spectralis segmentation algorithm in a semi-automated manner, with manual correction of any gross errors. Macular and GCL+IPL thickness measures were assessed and reported in the standard Early Treatment Diabetic Retinopathy Study (ETDRS) grid. Scans with an insufficient signal-to-noise ratio or a failure in the retinal thickness algorithm were either repeated or excluded from the analysis. All images met the required quality standards (OSCAR-IB criteria) (Tewarie et al., 2012) and were acquired and reported according to the Advised Protocol for OCT Study Terminology and Elements (APOSTEL) recommendations (Aytulun et al., 2021; Cruz-Herranz et al., 2016).

2.4. Statistical analysis

Descriptive statistics were used to summarize the sociodemographic and clinical characteristics of the sample. Depending on data distribution, the differences between SSD patients and HCs in sociodemographic and retinal measures were assessed using Chi-squared ($\chi 2$), independent *t*-tests, or Mann-Whitney U tests. Inter-eye correlations were evaluated using Pearson or Spearman correlation coefficients. Given the high inter-eye correlations, all subsequent analyses were performed using data from the right eye only. Pearson or Spearman correlation coefficients were also performed to assess the association between retinal measurements and premorbid, clinical, course-related, and cognitive variables. Inter-group differences (SSD vs HCs) were explored for all the retinal measures. The relationship between the retinal measures (specifically pRNFL) and premorbid, functioning, clinical, and cognitive variables was explored only in SSD cases as it was not measured in HCs. Several multiple linear regression models were employed to examine the associations between these variables controlled by the effects of other covariables (sex, age, PANSS total score, duration of untreated psychosis, and antipsychotic equivalent dose). Assumptions of normality, multicollinearity, heteroscedasticity, and autocorrelation were confirmed in all the cases, and the Benjamini–Hochberg procedure was applied to control the false discovery rate at 5% and minimize the risk of type I errors (Benjamini and Hochberg, 1995). All statistical analyses were conducted using SPSS v25 and RStudio 2024.09.1 + 394 for Windows, with a significance level set at $p < 0.05$.

Table 1
Sociodemographic and clinical characteristics of the sample.

Variable		SSD (*n* = 26) n(%) / Mean (SD)	HCs (*n* = 25) n(%) / Mean (SD)	χ2 / t / Z	p
Gender	Female	14 (56,00)	13 (50,00)	0,184	0,668
	Male	11 (44,00)	13 (50,00)		
Age (in years)		31,9 (1,25)	32,69 (1,91)	0,411	0,683
Civil Status	Single	22 (87,50)	22 (86,36)	0,013	0,909
	Married	3 (12,50)	4 (13,64)		
Education Level	Basic	1 (4,17)	0 (0,00)	11,944	0,003
	High School	18 (70,83)	6 (23,81)		
	University	6 (25,00)	20 (76,19)		
Occupation	Not Working	15 (58,33)	2 (9,09)	12,27	<0,001
	Working	10 (41,67)	24 (90,91)		
Socioeconomic Status	5	5 (21,74)	10 (40,00)	6,245	0,044
	4	5 (21,74)	13 (50,00)		
	≤3	14 (56,52)	3 (10,00)		
Alcohol	No	7 (29,17)	7 (27,27)	0,02	0,887
	Ever	18 (70,83)	19 (72,73)		
Smoking	No	13 (50,00)	7 (28,57)	2,143	0,143
	Ever	13 (50,00)	19 (71,43)		
Cannabis	No	12 (47,83)	21 (81,82)	5,67	0,017
	Ever	13 (52,17)	5 (18,18)		
BMI		25,49 (1,36)	22,45 (0,65)	−2,409	0,022
Mean BP		85,21 (1,92)	90,36 (1,89)	1,797	0,066
Antipsychotic Treatment	Oral	4 (15,38)	–	–	–
	LAI	20 (76,92)			
	No	2 (7,69)			
Adherence	Poor	13 (50,00)	–	–	–
	Optimal	13 (50,00)			
Premorbid Adjustment	Childhood Subscale	5,07 (0,85)	–	–	–
	Adolescence Subscale	8,67 (1,37)			
	Total Score	13,73 (1,97)			
GAF		70,00 (4,36)	–	–	–
Duration of Untreated Psychosis (months)		24,80 (13,83)			
Time since diagnosis (months)		32,50 (22,29)	–	–	–
PANSS	Positive Subscale	10,20 (0,78)	–	–	–
	Negative Subscale	14,00 (1,88)			

(*continued on next page*)

Table 1 (*continued*)

Variable		SSD (n = 26) n(%) / Mean (SD)	HCs (n = 25) n(%) / Mean (SD)	χ2 / t / Z	p
	General Psychopathology Subscale	25,93 (1,85)			
	Total Score	49,93 (3,95)			
Antipsychotic dose (Risperidone eq. mg.)		6,09 (1,51)	–	–	–
Emotional Intelligence (MSCEIT)		106,56 (21,38)	–	–	–
Working Memory (Letter–Number)		40,27 (6,6)	–	–	–
Verbal Memory (CVLT)*		−0,56 (0,92)	–	–	–
Executive Function (WCST)*		0,14 (0,69)	–	–	–
Processing Speed (TMT-A)		54,42 (9,82)	–	–	–
Sustained Attention (CPT)*		−0,23 (1,03)	–	–	–

BMI, Body Mass Index; BP, Blood Pressure; CGI, Clinical Global Impression; LAI, Long Acting Injectables; Eq.mg., Equivalent milligrams; FAST, Functional Assessment Short Test; GAF, Global Assessment of Functioning; HCs, Healthy Controls; PANSS, Positive and Negative Syndrome Scale; SD, Standard Deviation; SSD, Schizophrenia Spectrum Disorders.
**PCA based data.*

3. Results

3.1. Participants

Table 1 presents the sociodemographic and clinical characteristics of SSD cases (n = 26) and HCs (n = 25). No significant inter-group differences were found in terms of age, sex, marital status, alcohol use, and mean BP. However, significant differences were observed in educational level ($\chi2$=11.944,p = 0.003), occupation ($\chi2$=12.27,p < 0.001), socioeconomic status (SES) ($\chi2$=6.245,p = 0.044), cannabis use ($\chi2$=5.67,p = 0.017) and body mass index (BMI) (t=−2.409,p = 0.022). Specifically, patients showed a lower educational/occupational level and SES, and higher BMI and cannabis use on average. Most of the patients were under antipsychotic treatment, especially oral medication, with a mean antipsychotic dose of 6.09 mg (SD=1.51, Risperidone equivalent mg). The mean time since diagnosis in cases was 32.50 months (SD=22.29), while the mean DUP was 24.80 months (SD=13.83) (Table 1).

Comparisons between retinal measurements of SSD cases and HCs revealed several significant differences. In the right eye (OD), patients showed a significantly higher average thickness of the pRNFL compared to HCs (t=−2.255,p = 0.029), as well as in the left eye (OS) (t=−2.085,p = 0.044). Additionally, significant differences were observed in superior temporal pRNFL thickness (OD: t=−2.043,p = 0.047; OS: t=−2.244,p = 0.029) (Table 2). However, other retinal measurements, such as macular volume, total and quadrants macular thickness, and GCL+IPL thickness, did not show significant differences between the groups. Hence, subsequent analyses in SSD cases were performed only for pRNFL measures. Furthermore, high inter-eye correlations were found in all retinal measures (Supplementary Table S2), so all successive analyses were conducted only in the right eye.

Table 2
Differences between cases (SSD) and healthy controls (HCs) in retinal measures.

Variable	OD				OS			
pRNFL	**SSD (n = 26) Mean (SD)**	**HCs (n = 25) Mean (SD)**	**t-Z**	**p**	**SSD (n = 26) Mean (SD)**	**HCs (n = 25) Mean (SD)**	**t-Z**	**p**
Average Thickness	107,72 (2,07)	102,12 (1,41)	−2,255	0,029*	105,60 (1,98)	100,77 (1,21)	−2,085	0,044*
Superior Nasal	113,04 (4,12)	109,50 (2,72)	−0,723	0,473	120,48 (3,91)	112,15 (3,58)	−1,575	0,122
Nasal	82,44 (3,09)	77,81 (3,02)	−1,376	0,169	76,20 (2,95)	75,27 (2,74)	−0,232	0,818
Inferior Nasal	129,28 (5,56)	118,08 (4,38)	−1,589	0,119	127,52 (5,42)	120,88 (3,95)	−0,994	0,325
Inferior Temporal	154,40 (3,91)	149,62 (2,49)	−1,040	0,303	154,96 (3,50)	152,00 (2,76)	−0,667	0,508
Temporal	73,48 (2,11)	69,00 (1,68)	−1,632	0,103	70,72 (1,79)	66,50 (1,62)	−1,75	0,086
Superior Temporal	153,36 (3,33)	145,19 (2,21)	−2,043	0,047*	147,6 (3,33)	138,35 (2,47)	−2,244	0,029*
Macula	**SSD (n = 26) Mean (SD)**	**HCs (n = 25) Mean (SD)**	**t-Z**	**p**	**SSD (n = 26) Mean (SD)**	**HCs (n = 25) Mean (SD)**	**t-Z**	**p**
Total Volume	8,66 (0,09)	8,73 (0,07)	0,675	0,503	8,70 (0,08)	8,77 (0,07)	0,652	0,517
Foveal Thickness	266,44 (3,94)	274,77 (4,19)	1,446	0,155	267,72 (4,08)	275,96 (4,29)	1,389	0,171
Inner Superior	343,24 (3,19)	346,62 (3,07)	0,763	0,449	344,32 (3,05)	349,12 (3,35)	1,057	0,296
Inner Nasal	341,28 (3,32)	347,96 (3,51)	1,382	0,173	345,16 (2,93)	350,81 (3,62)	1,208	0,233
Inner Inferior	338,44 (3,03)	345,31 (2,99)	1,611	0,114	339,24 (2,88)	345,19 (3,03)	1,424	0,161
Inner Temporal	328,72 (2,96)	332,38 (2,94)	0,878	0,384	326,00 (3,04)	332,46 (3,24)	1,453	0,153
Outer Superior	301,72 (3,25)	302,23 (2,44)	0,126	0,900	304,96 (3,16)	304,46 (2,63)	−0,122	0,904
Outer Nasal	320,04 (3,33)	321,69 (3,23)	−0,047	0,962	316,24 (3,39)	319,50 (3,14)	0,706	0,483
Outer Inferior	287,00 (3,04)	291,27 (2,39)	1,109	0,273	288,64 (2,72)	292,08 (2,45)	−0,509	0,611
Outer Temporal	283,88 (3,45)	284,42 (2,53)	0,128	0,899	290,08 (2,97)	288,92 (2,73)	−0,287	0,775
GCL+IPL	**SSD (n = 26) Mean (SD)**	**HCs (n = 25) Mean (SD)**	**t-Z**	**p**	**SSD (n = 26) Mean (SD)**	**HCs (n = 25) Mean (SD)**	**t-Z**	**p**
Central Thickness	35,20 (1,37)	37,08 (1,84)	0,812	0,421	35,88 (1,28)	37,46 (1,90)	0,691	0,493
Inner Superior	94,68 (1,29)	96,65 (1,12)	1,159	0,252	95,08 (1,40)	97,04 (1,19)	1,067	0,291
Inner Nasal	93,44 (1,56)	96,65 (1,56)	1,460	0,151	97,12 (1,36)	99,42 (1,35)	1,201	0,236
Inner Inferior	94,36 (1,35)	97,00 (1,27)	1,426	0,160	94,64 (1,29)	96,81 (1,33)	1,170	0,248
Inner Temporal	91,44 (1,36)	92,62 (1,42)	0,597	0,553	87,08 (1,41)	90,42 (1,68)	1,515	0,136
Outer Superior	65,28 (1,21)	65,31 (0,95)	−0,236	0,813	65,84 (1,16)	65,58 (0,76)	−0,699	0,484
Outer Nasal	71,64 (1,25)	70,12 (1,22)	−0,873	0,387	67,76 (1,37)	67,46 (0,97)	−0,179	0,859
Outer Inferior	60,44 (1,11)	61,15 (0,86)	0,509	0,613	60,00 (1,05)	61,00 (0,87)	0,734	0,466
Outer Temporal	69,64 (1,53)	69,00 (1,03)	−0,347	0,730	72,28 (1,31)	70,85 (1,09)	−0,844	0,403

GCL+IPL, Ganglion Cell, and Inner Plexiform Layer; HCs, Healthy Controls; OD, Right Eye; OS, Left Eye; pRNFL, Peripapillary Retinal Nerve Fiber Layer; SD, Standard Deviation; SSD, Schizophrenia Spectrum Disorders.

Table 3
Associations between pRNFL, premorbid adjustment (PAS) and functionality (GAF) in SSD cases ($n = 26$).

		PAS				GAF			
		Beta	p	pFDR	R^2	Beta	p	pFDR	R^2
Average Thickness	Independent variable	-0,642	0,166	0,398	0,409	0,479	0,154	0,398	0,418
	Sex	2,846	0,659	0,901		0,868	0,888	0,959	
	Age	-0,487	0,321	0,672		-0,131	0,792	0,948	
	DUP	-0,007	0,340	0,670		-0,008	0,276	0,611	
	PANSS	0,050	0,813	0,940		0,260	0,392	0,729	
	AP dose	-0,615	0,283	0,611		-0,215	0,719	0,927	
Superior Nasal	Independent variable	-0,927	0,315	0,812	0,327	0,437	0,523	1,011	0,271
	Sex	16,864	0,222	0,783		13,731	0,315	0,812	
	Age	-0,454	0,644	1,003		-0,079	0,941	1,019	
	DUP	-0,009	0,545	0,995		-0,009	0,549	0,995	
	PANSS	0,012	0,978	0,993		0,131	0,838	1,068	
	AP dose	-0,168	0,882	1,055		0,216	0,866	1,063	
Nasal	Independent variable	-1,687	0,024	0,180	0,512	0,910	0,124	0,641	0,301
	Sex	4,544	0,626	1,088		-1,037	0,923	0,966	
	Age	-0,086	0,900	0,957		0,659	0,455	1,071	
	DUP	-0,005	0,634	1,050		-0,006	0,621	1,133	
	PANSS	0,413	0,204	0,854		0,711	0,193	0,854	
	AP dose	-0,707	0,385	1,243		0,077	0,941	0,965	
Inferior Nasal	Independent variable	-2,210	0,079	0,484	0,377	0,691	0,488	1,817	0,122
	Sex	6,338	0,706	1,300		-1,526	0,937	0,985	
	Age	-0,488	0,695	1,383		0,215	0,890	1,060	
	DUP	-0,003	0,877	1,114		-0,002	0,924	1,026	
	PANSS	0,144	0,797	1,161		0,173	0,852	1,119	
	AP dose	-0,495	0,731	1,232		0,150	0,936	0,996	
Inferior Temporal	Independent variable	-0,510	0,545	0,888	0,388	0,374	0,542	0,890	0,389
	Sex	2,735	0,824	1,004		1,156	0,922	1,013	
	Age	-1,394	0,152	0,464		-1,115	0,265	0,590	
	DUP	-0,008	0,557	0,888		-0,009	0,523	0,898	
	PANSS	0,056	0,891	0,995		0,218	0,704	0,975	
	AP dose	-1,304	0,238	0,550		-0,991	0,400	0,744	
Temporal	Independent variable	1,036	0,021	0,156	0,638	-0,185	0,629	0,986	0,288
	Sex	-6,874	0,232	0,577		-3,036	0,684	0,944	
	Age	-0,231	0,575	0,966		-0,484	0,431	0,805	
	DUP	-0,005	0,368	0,725		-0,006	0,452	0,819	
	PANSS	-0,242	0,209	0,574		-0,155	0,667	0,993	
	AP dose	-0,851	0,100	0,393		-1,048	0,173	0,505	
Superior Temporal	Independent variable	-0,206	0,814	0,909	0,202	1,010	0,080	0,337	0,464
	Sex	1,778	0,890	0,905		2,091	0,838	0,920	
	Age	-0,732	0,451	0,687		-0,151	0,855	0,917	
	DUP	-0,012	0,405	0,661		-0,016	0,185	0,434	
	PANSS	-0,190	0,659	0,833		0,496	0,328	0,594	
	AP dose	0,321	0,772	0,877		1,103	0,283	0,555	

AP dose, antipsychotic dose (in Risperidone equivalent mg); DUP, Duration of Untreated Psychosis; GAF, Global Assessment of Functioning Scale; PAS, Cannon-Spoor Premorbid Adjustment Scale; PANSS, Total Score; pFDR, corrected p-value (False Discovery Rate), Benjamini–Hochberg Procedure; pRNFL, Peripapillary Retinal Nerve Fiber Layer; SSD, Schizophrenia Spectrum Disorders.

The influence of baseline sociodemographic characteristics was explored across the whole sample. No significant associations were found between sex and pRNFL measures, but with foveal thickness, macular inner ring quadrants, and central and inner temporal GCL+IPL thickness (Supplementary Table S3). Smoking also did not show significant associations with pRNFL thickness, but macula central and inner ring thickness and GCL+IPL central thickness (Supplementary Table S3). Other sociodemographic variables showed no association with any given retinal measure.

3.2. Premorbid adjustment, functioning, and clinical variables in cases

Significant associations were found between Premorbid Adjustment and nasal pRNFL (β=−1.687,$p = 0.024$) and temporal pRNFL (β=1.036, $p = 0.021$), controlled by sex, age, duration of untreated psychosis, PANSS total score, and antipsychotic dose in cases. However, these results did not remain significant after correcting for multiple testing (pFDR=0.180 and pFDR=0.156, respectively) (Table 3). Functioning, duration of untreated psychosis, time since diagnosis (in months), and PANSS total score showed no significant association with pRNFL (Table 3 and Supplementary Tables S4 and S5).

3.3. Cognition in cases

Associations between pRNFL and cognitive variables in cases corrected by sex, age, PANSS total score, and antipsychotic dose are presented in Tables 4 and 5. Significant associations were found between emotional intelligence and superior temporal pRNFL (β=−0.733,$p = 0.033$) and temporal pRNFL (β=−0.256,$p = 0.042$), although in this case age also showed a significant association (β=2.423,$p = 0.007$). Working memory also was significantly associated with superior temporal pRNFL (β=−1.799,$p = 0.027$). Executive function was significantly associated with superior nasal pRNFL (β=−15.624,$p = 0.037$), but sex also showed a significant association (β=21.790,$p = 0.044$). Processing speed was significantly associated with average pRNFL at the expense of the Superior Temporal quadrant (β=−0.945,$p = 0.042$), although in the first case, age also showed a statistically significant association (β=−1139,$p = 0,017$). Verbal memory and sustained attention showed no association with any pRNFL measures. The associations were lost after correcting for multiple analyses (Tables 4 and 5).

4. Discussion

This study found that patients with early-course schizophrenia

Table 4
Associations between retinal variables and cognitive domains: Emotional Intelligence, Working Memory, and Verbal Memory in SSD cases ($n = 26$).

		Emotional Intelligence (MSCEIT)				Working Memory (Letter–Number)				Verbal Memory (CVLT)			
		Beta	p	pFDR	R2	Beta	p	pFDR	R2	Beta	p	pFDR	R2
Average Thickness	Independent variable	-0,253	0,115	0,359	0,909	-0,805	0,070	0,294	0,703	-4,409	0,140	0,408	0,647
	Sex	1,368	0,777	0,947		7,018	0,208	0,480		9,273	0,092	0,343	
	Age	-1,281	0,105	0,351		-0,862	0,102	0,351		-0,918	0,078	0,307	
	PANSS	-0,195	0,472	0,753		-0,011	0,940	0,979		-0,009	0,950	0,968	
	AP dose	0,234	0,592	0,845		0,079	0,855	0,954		0,287	0,528	0,804	
Superior Nasal	Independent variable	0,040	0,943	1,011	0,563	-1,143	0,278	0,883	0,473	-5,484	0,427	0,964	0,474
	Sex	19,368	0,398	0,953		20,679	0,163	0,607		25,884	0,062	0,296	
	Age	-3,035	0,309	0,872		-0,620	0,615	1,042		-0,893	0,439	0,950	
	PANSS	0,248	0,830	1,079		0,090	0,820	1,090		0,036	0,923	1,034	
	AP dose	0,117	0,951	1,008		0,312	0,782	1,101		0,623	0,575	1,014	
Nasal	Independent variable	-0,142	0,558	1,101	0,816	-0,849	0,317	1,180	0,266	-4,328	0,443	1,089	0,238
	Sex	-9,191	0,346	1,221		2,612	0,813	1,068		7,823	0,440	1,100	
	Age	-2,499	0,095	0,533		-0,449	0,653	0,996		-0,743	0,433	1,134	
	PANSS	-0,098	0,839	1,019		0,150	0,642	1,033		0,079	0,796	1,103	
	AP dose	0,189	0,813	1,030		0,291	0,750	1,069		0,550	0,547	1,133	
Inferior Nasal	Independent variable	0,135	0,839	1,119	0,638	-1,218	0,451	1,974	0,155	-2,390	0,828	1,125	0,154
	Sex	-12,883	0,621	1,562		-1,579	0,941	0,978		8,542	0,667	1,495	
	Age	-4,133	0,256	1,431		-0,536	0,781	1,202		-1,355	0,472	1,875	
	PANSS	-0,758	0,590	1,674		-0,093	0,881	1,093		-0,294	0,630	1,562	
	AP dose	0,339	0,881	1,074		0,428	0,809	1,144		0,760	0,674	1,418	
Inferior Temporal	Independent variable	-0,668	0,174	0,485	0,776	-0,985	0,273	0,590	0,346	-8,061	0,158	0,462	0,665
	Sex	5,041	0,750	0,948		12,323	0,309	0,591		13,009	0,199	0,493	
	Age	-1,412	0,494	0,894		-2,222	0,067	0,281		-1,996	0,053	0,251	
	PANSS	-0,463	0,593	0,899		-0,019	0,956	1,014		0,058	0,842	1,008	
	AP dose	0,588	0,677	0,987		-0,276	0,773	0,959		0,002	0,998	0,998	
Temporal	Independent variable	-0,256	0,042	0,236	0,965	0,110	0,873	0,944	0,332	0,222	0,964	0,980	0,209
	Sex	5,464	0,154	0,491		2,033	0,828	0,994		-2,221	0,800	1,011	
	Age	2,423	0,007	0,076		-0,475	0,577	0,965		-0,142	0,862	0,968	
	PANSS	-0,337	0,117	0,414		-0,115	0,675	0,955		-0,013	0,960	0,993	
	AP dose	-0,402	0,214	0,574		-0,806	0,318	0,688		-0,890	0,285	0,671	
Superior Temporal	Independent variable	-0,733	0,033	0,185	0,916	-1,799	0,027	0,167	0,775	-10,165	0,112	0,374	0,552
	Sex	3,823	0,645	0,856		14,441	0,138	0,384		14,923	0,180	0,444	
	Age	-1,462	0,219	0,458		-1,426	0,109	0,392		-1,181	0,248	0,503	
	PANSS	0,304	0,505	0,720		-0,176	0,501	0,730		-0,055	0,862	0,917	
	AP dose	1,092	0,199	0,440		1,228	0,128	0,391		1,627	0,117	0,374	

AP dose, antipsychotic dose (in Risperidone equivalent mg); CVLT, California Verbal Learning Test; Letter–Number, Letter–Number Sequencing Subtest of the WAIS-III; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; PANSS, Total score; pFDR, corrected p-value (False Discovery Rate), Benjamini–Hochberg Procedure; pRNFL, Peripapillary Retinal Nerve Fiber Layer; SSD, Schizophrenia Spectrum Disorders.

spectrum disorders (SSD) exhibited significant retinal structural differences compared to healthy controls (HCs). Specifically, increased peripapillary retinal nerve fiber layer (pRNFL) thickness was observed in several quadrants, notably in the superior temporal quadrant. This may reflect a complex interplay of neurodegenerative and neuroinflammatory processes. Several authors have proposed that this retinal thickening might be more pronounced in the early stages of schizophrenia or during acute episodes, where neuroinflammation is at its peak, potentially masking the tissue loss that becomes more evident as the disease progresses (Ascaso et al., 2015; Lai et al., 2020; Shew et al., 2024). Besides, certain studies suggest that the increased thickness could also be due to antipsychotic medication effects, which might induce changes in retinal structure through dopaminergic or other neurochemical pathways (Altun et al., 2021). However, since higher doses of antipsychotics are typically prescribed in response to more severe clinical presentations, it remains unclear whether these changes are a consequence of any of these subjacent factors (Ilzarbe and Vieta, 2023).

Previous studies have also shown similar findings, including those by Alizadeh et al., who reported that the retinal nerve fiber layer (RNFL) might be thicker during the early stages of schizophrenia and thins as the disease stabilizes or progresses (Alizadeh et al., 2021). Additionally, studies by Asanad et al. and Liu et al. have highlighted the role of inflammatory processes and cognitive decline in retinal structural changes in schizophrenia, further supporting the idea that retinal thickening could be an early marker of disease-related neuroinflammatory changes (Asanad et al., 2021; Liu et al., 2020). The lack of an apparent correlation with illness duration in this study may be due to the sample's relatively homogeneous nature, consisting of individuals with<5 years since diagnosis. Differences between this group and those with more chronic conditions would likely become more evident in a more prolonged illness trajectory cohort.

Another key finding of this study is the significant association between premorbid adjustment and nasal and temporal pRNFL thickness. These results underscore the potential role of early-life social and academic functioning in the neurodevelopmental trajectory of SSD (Shapiro et al., 2009). This is consistent with findings that early-life adversities and neurodevelopmental insults may result in lasting changes in the central nervous system and the retina, an extension of the brain's neural circuitry (Lai et al., 2020; Shew et al., 2024). This also aligns with evidence from studies showing that individuals with a history of developmental delays or suboptimal early cognitive and social functioning exhibit distinct retinal changes (Alizadeh et al., 2021; Ascaso et al., 2010).

Our study also revealed significant associations between retinal measures and cognitive performance. Specifically, the pRNFL thickness was associated with emotional intelligence, working memory, executive function, and processing speed. These correlations were significant in the global pRNFL and its temporal and nasal quadrants. The relationship between retinal structure and cognition, although still underexplored in the literature (Gonzalez-Diaz et al., 2022), suggests that retinal imaging could be a non-invasive tool to monitor cognitive status in SSD patients. In consequence, the pRNFL may serve as a proxy for cortical atrophy and loss of white matter integrity, which is known to contribute to cognitive deficits in SSD (Celik et al., 2016; Haijma et al., 2013), as reported in several neurodegenerative disorders previously (Alves et al., 2023; Chan et al., 2019; Chrysou et al., 2019; den Haan et al., 2017; Gordon-Lipkin

Table 5
Associations between retinal variables and cognitive domains: Executive Function, Processing Speed, and Sustained Attention in SSD cases ($n = 26$).

		Executive Function (WCST)				Processing Speed (TMT-A)				Sustained Attention (CPT)			
		Beta	p	pFDR	R2	Beta	p	pFDR	R2	Beta	p	pFDR	R2
Average Thickness	Independent variable	-5,350	0,151	0,406	0,641	-0,439	0,040	0,219	0,742	2,127	0,429	0,757	0,553
	Sex	7,850	0,151	0,398		9,241	0,057	0,275		9,569	0,118	0,359	
	Age	-0,967	0,065	0,288		-1,139	0,017	0,101		-1,365	0,043	0,219	
	PANSS	-0,047	0,758	0,940		0,082	0,558	0,813		-0,041	0,806	0,940	
	AP dose	-0,028	0,953	0,959		0,126	0,741	0,937		0,313	0,554	0,813	
Superior Nasal	Independent variable	-15,624	0,037	0,247	0,702	-0,499	0,342	0,849	0,495	-8,817	0,105	0,440	0,612
	Sex	21,790	0,044	0,251		25,845	0,058	0,296		24,463	0,045	0,251	
	Age	-0,673	0,432	0,950		-1,168	0,290	0,883		-0,210	0,845	1,068	
	PANSS	-0,011	0,968	0,993		0,136	0,727	1,083		-0,029	0,926	1,034	
	AP dose	-0,138	0,873	1,055		0,430	0,689	1,049		0,008	0,994	0,994	
Nasal	Independent variable	-5,998	0,390	1,189	0,256	-0,595	0,147	0,702	0,396	-0,305	0,950	0,959	0,167
	Sex	6,233	0,537	1,145		7,793	0,390	1,164		7,740	0,465	1,039	
	Age	-0,768	0,406	1,133		-0,962	0,246	0,970		-0,924	0,399	1,133	
	PANSS	0,042	0,887	0,982		0,216	0,464	1,039		0,042	0,894	0,957	
	AP dose	0,210	0,821	1,018		0,367	0,648	1,017		0,440	0,654	0,996	
Inferior Nasal	Independent variable	-5,191	0,703	1,314	0,166	-0,520	0,534	1,739	0,197	-1,391	0,882	1,065	0,15
	Sex	7,177	0,720	1,256		8,527	0,660	1,542		8,305	0,677	1,411	
	Age	-1,309	0,476	1,817		-1,477	0,402	1,954		-1,322	0,523	1,788	
	PANSS	-0,315	0,600	1,609		-0,162	0,797	1,153		-0,317	0,600	1,601	
	AP dose	0,495	0,790	1,186		0,630	0,718	1,269		0,631	0,735	1,232	
Inferior Temporal	Independent variable	-3,927	0,604	0,899	0,565	-0,698	0,104	0,386	0,697	8,546	0,064	0,281	0,732
	Sex	11,926	0,299	0,588		12,950	0,181	0,485		14,279	0,126	0,440	
	Age	-2,270	0,050	0,251		-2,400	0,018	0,099		-3,318	0,006	0,038	
	PANSS	-0,009	0,977	0,996		0,195	0,518	0,898		0,010	0,968	1,007	
	AP dose	-0,332	0,747	0,948		-0,276	0,736	0,962		0,313	0,697	0,983	
Temporal	Independent variable	3,228	0,590	0,965	0,243	0,157	0,675	0,962	0,229	6,068	0,107	0,398	0,468
	Sex	-1,383	0,874	0,944		-2,221	0,798	1,012		-1,271	0,860	0,979	
	Age	-0,233	0,769	1,011		-0,130	0,867	0,959		-0,788	0,306	0,684	
	PANSS	-0,011	0,965	0,980		-0,057	0,840	0,988		0,002	0,993	0,993	
	AP dose	-0,752	0,368	0,725		-0,861	0,291	0,671		-0,542	0,433	0,805	
Superior Temporal	Independent variable	-13,011	0,099	0,389	0,565	-0,945	0,042	0,215	0,65	7,357	0,188	0,434	0,494
	Sex	11,468	0,291	0,541		14,849	0,138	0,384		15,990	0,178	0,447	
	Age	-1,274	0,204	0,440		-1,691	0,070	0,313		-2,478	0,058	0,280	
	PANSS	-0,141	0,652	0,842		0,136	0,654	0,833		-0,123	0,714	0,850	
	AP dose	0,874	0,380	0,667		1,267	0,158	0,422		1,825	0,111	0,374	

AP dose, antipsychotic dose (in Risperidone equivalent mg); CPT, Conners' Continuous Performance Test; PANSS, Total score; pFDR, corrected p-value (False Discovery Rate), Benjamini–Hochberg Procedure; pRNFL, Peripapillary Retinal Nerve Fiber Layer; SSD, Schizophrenia Spectrum Disorders; TMT-A, Trail Making Test Form A; WCST, Wisconsin Card Sorting Test.

et al., 2007; Petzold et al., 2010; Rifai et al., 2021; Siger et al., 2008). Specifically, the observed inverse correlation suggests that a concurrent progressive loss of retinal nerve fiber layer thickness might appear as the disease progresses, reflecting a broader neurodegenerative trajectory.

Nonetheless, as cognitive impairments often emerge before symptom onset and remain stable over time, neurodevelopmental disruptions might be more plausible than a progressive decline (Bora and Murray, 2014; Watson et al., 2022). However, a subset of patients with more severe illness, inpatient status, and lower educational attainment may experience a more evident neurodegenerative trajectory (Irani et al., 2011). Given the relatively non-invasive and cost-effective nature of OCT imaging, incorporating retinal assessments could offer a valuable adjunctive measure for cognitive monitoring in SSD. This approach could help in the early identification of cognitive dysfunction, allowing for timely interventions that might mitigate further deterioration (Bernardo et al., 2013; Gonzalez-Diaz et al., 2021). The consistency of these findings with previous studies that report similar associations underscores the growing importance of retinal imaging in psychiatric research and its potential role in future clinical applications (Komatsu et al., 2022; Lai et al., 2020). However, the lack of consistent findings across all retinal parameters in this study indicates that retinal imaging should be considered a complementary tool rather than a standalone diagnostic or monitoring method. These mixed results highlight the need for caution when interpreting the findings, given the modest p-values (many of which became non-significant after multiple analysis corrections) and the exploratory nature of this study. The absence of significant differences in many retinal measures underscores the importance of further research to validate and expand on these preliminary observations. A limitation of this study is the lack of correction for multiple comparisons in the initial case-control analyses. However, this decision reflects the exploratory purpose of these comparisons and the need to conserve statistical power in identifying retinal measures of interest for further investigation. Furthermore, many of the associations found in this study were lost after correcting for multiple comparisons, as previously reported by Carriello et al. in a similar study (Carriello et al., 2023).

Besides, the cross-sectional design of this study also precludes inferring causality between retinal changes and clinical outcomes (Vieta and De Prisco, 2024), and its relatively small sample size, while comparable to other studies in this field, may limit the generalizability of the findings (De Prisco and Vieta, 2024). As visual memory was not assessed in the sample, a comprehensive understanding of the cognitive impairments typically observed in SSD might also be restricted. Besides, functional and cognitive performance was not comprehensively explored in HCs; hence, it was not included in the analyses. We also acknowledge that excluding processing speed, working memory, and emotional intelligence measures from the PCA may be considered a limitation. However, including single-measure domains in the PCA could dilute the interpretability and stability of the derived factors, particularly in a study with a relatively small sample size.

Furthermore, the absence of OCT-Angiography data prevents a more thorough evaluation of retinal microvascular changes that could complement the structural findings. Therefore, larger sample sizes are still needed for longitudinal and multimodal studies (involving functional, structural and vascular retinal evaluation, brain imaging and peripheral inflammatory markers). However, using advanced retinal imaging

techniques and the comprehensive assessment of cognitive, functional, and clinical variables add value to this study. Additionally, including premorbid adjustment and DUP as variables of interest provides a novel perspective on the neurodevelopmental aspects of SSD.

In conclusion, this study suggests that retinal structural alterations, particularly in the pRNFL, macular, and GCL+IPL layers, are present in patients with SSD and are significantly associated with premorbid, functional, and cognitive performance. This study highlights the potential of retinal imaging as a complementary biomarker for investigating neurodevelopmental and cognitive alterations in schizophrenia spectrum disorders (SSD). However, these findings are preliminary and limited by the small sample size. Future studies with larger, more diverse cohorts and longitudinal designs are essential to validate these preliminary findings and clarify the clinical relevance of retinal biomarkers in SSD.

Contributors

JMG and MB conceptualized the study. JMG, BSD, ACC, SA, and MB designed the study and JMG wrote the protocol. JMG, SAA, MFF, MSN, SS, and APR, acquired the data. JMG and SA undertook the statistical analysis. JMG wrote the first draft of the manuscript, and SA, EV, CT, and MB revised it. All authors revised and contributed to the consecutive versions of the manuscript and approved the final manuscript.

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Declaration of competing interest

JGD has been a consultant for, received honoraria from, and/or been on the speakers/advisory board of Janssen, Eurofarma, Servier, Sanofi, Lilly, and Pfizer, outside the submitted work. BSD has been a consultant for, and received honoraria from Chiesi and Santhera, outside the submitted work. SA has been a consultant to and/or has received honoraria/grants from Otsuka-Lundbeck, with no financial or other relationship relevant to the subject of this article. EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Beckley-Psytech, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, HMNC, Idorsia, Johnson & Johnson, Lundbeck, Luye Pharma, Medincell, Merck, Newron, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatris, outside the submitted work. MB has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of Abartis Pharma, ABBiotics, Adamed, Angelini, Casen Recordati, Esteve Pharmaceuticals, Janssen-Cilag, Menarini, Rovi, Takeda and Viatris, outside the submitted work. The rest of the authors report no biomedical financial interests or potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2024.12.006.

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