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Neuropsychological and clinical correlations of optical coherence tomography findings in patients with schizophrenia

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ABSTRACT

Objective: There are increasing studies examining retinal fiber layer (RNFL) and ganglion cell layer (GCL) thinning in patients with schizophrenia. However, the results are controversial, and clinical and cognitive reflections of these findings remain unclear. With this study, we aim to examine retinal abnormalities and establish correlations with cognitive and clinical parameters.

Methods: In this cross-sectional study, we examined 29 patients with schizophrenia and 13 age and gender-matched healthy controls. All participants underwent psychometric assessment, neuropsychological tests, and optical coherence tomography (OCT) measurements. The retinal fiber layer and ganglion cell layer thickness were used as retinal parameters.

Results: Five patients dropped out during the OCT measurement process, 24 patients with schizophrenia and nine healthy controls were included in the analysis. There was no statistically significant difference between groups in measuring retinal nerve fiber layer or ganglion cell layer thicknesses. The verbal fluency test score negatively correlated with left RNFL superior ($\rho = -.422$, $p < .05$). STROOP response duration positively correlated with right RNFL on average ($\rho = .551$, $p < .05$), left RNFL on average ($\rho = .498$, $p < .05$), right RNFL superior ($\rho = .507$, $p < .05$), left RNFL superior ($\rho = .461$, $p < .05$) and right RNFL temporal values ($\rho = .434$, $p < .05$). STROOP response error was also positively correlated with right RNFL temporal thickness ($\rho = .430$, $p < .05$). STROOP response duration was positively correlated with right GCL total ($\rho = .646$, $p < .01$), right GCL superior ($\rho = .658$, $p < .01$) and right GCL inferior ($\rho = .596$, $p < .01$) thickness.

Conclusion: We did not find a significant relationship between reduced RNFL or GCL thickness and cognitive impairment. However, we had several positive correlations between cognitive task scores and RNFL and GCL thicknesses. Additionally, our study did not correlate symptom severity and clinical severity parameters with reduced RNFL or GCL thickness.

Keywords: schizophrenia, OCT, retina, cognitive impairment, clinical severity

1. INTRODUCTION

Schizophrenia is a life-long mental disorder, the pathophysiology of which has not yet been clarified, causing significant deterioration in the individual's functionality and quality of life. In addition to the positive and negative symptoms observed in schizophrenia patients, cognitive deficiency constitutes one of the main symptom clusters of the disease. Studies have revealed that patients with schizophrenia have widespread impairments in many cognitive domains, such as executive functions, attention, verbal learning, memory, and verbal fluency, and have shown that cognitive dysfunction seen in schizophrenia predicts poor functionality and inadequate treatment response (1-3).

Recent meta-analyses have shown that the initial level of functionality and early diagnosis and treatment are the most important predictors of a patient's functionality and emphasized the importance of biomarkers that can be detected early in schizophrenia (4, 5). In addition to numerous structural and functional neuroimaging studies conducted for this purpose, studies examining retinal structure changes in patients with schizophrenia have increased. Retinal evaluation is suggested as a candidate biomarker for schizophrenia (6-8). Optical coherence tomography (OCT) is an easy-to-apply, non-invasive retinal imaging method that has come to the forefront and gives information about retinal nerve fiber layer thicknesses, macular volume, and macular thickness, which provides an idea about many neurodegenerative processes so far (9-12). Although thinning of the peripapillary retinal nerve fiber layers (pRNFL) has been shown in several OCT examinations performed in patients with schizophrenia to date (13, 14), studies examining the relationship of retinal

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changes with clinical symptoms or cognitive functions are limited and revealed inconsistent results (15-17). With this study, firstly, we aim to compare the RNFL and ganglion cell layer (GCL) thickness between patients and healthy controls. Secondly, we aim to elucidate the relationship between clinical and cognitive impairments and retinal alterations that may occur in patients with schizophrenia.

2. METHODS

2.1. Sample and Study Procedure

In this cross-sectional study, researchers evaluated a consecutive series of 50 patients with schizophrenia who were under treatment at the Marmara University Hospital's psychiatry outpatient clinic in Istanbul, Turkey. Diagnosis of schizophrenia was made through several sessions with two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria (DSM 5, APA 2013). Patients aged 18-50 who had been stable clinically for at least three months were referred to the research psychiatrist after a routine psychiatric evaluation. Subjects with mental retardation, alcohol, and substance use disorder, history of head trauma leading to unconsciousness, and degenerative neurological, immunological, or systemic disease that may affect the visual pathways were excluded from the study. Also, 20 healthy controls matched with patients regarding age, gender, and education were recruited for the study. After the first evaluation, individuals who met the inclusion criteria were subjected to ophthalmological examination. Participants who have a primary ophthalmologic disease (glaucoma, retinal disease, age-related macular degeneration, diabetic retinopathy, degenerative myopia); myopia, hyperopia, or astigmatism ≥1 diopter, and a pathology such as cataract, corneal leukoma or vitreous hemorrhage that may affect the ocular examination and optical coherence tomography measurement were not included to the study. Following the initial step, the sample consisted of 29 patients, and 13 healthy controls were invited within five days for psychometric and neurocognitive assessment and OCT measurement. The whole of the measurements was conducted on the same day of evaluation. Five patients dropped out during the OCT process, 24 patients with schizophrenia and nine healthy controls were included in the final analysis. The study followed the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice Guidelines. All participants provided written informed consent, and the local ethics committee approved the study (approval number: 09.2017.432).

2.2. Data acquisition

2.2.1. Psychometric Measures

The participants' sociodemographic features, patients' clinical information about the history of schizophrenia, and current clinical characteristics were obtained through a semi-structured data form developed by the research team. Psychopathological assessment was performed using The Positive and Negative Syndrome Scale for Schizophrenia (PANSS). The scale examines the severity of the disease under three subheadings: positive symptoms, negative symptoms, and general psychopathology. It evaluates 30 symptom-oriented items on a 7-point scale; 1 means 'absent' and 7 means 'excessive'. The range for the Positive and Negative Scales is 7-49, and the range for the General Psychopathology Scale is 16-112. The total PANSS score is simply the sum of the sub scales (18).

2.2.2. Assessment of Cognitive Functions

A battery of neuropsychological tests was designed to assess the impairments in various cognitive domains. Wechsler Memory Scale-Revised (WMS-R) and WMS-R visual reproduction subscale was utilized for assessing visual memory (19), Digit Span test was used to evaluate verbal attention and working memory (19), the Stroop Color–Word Interference Test (SCWIT) was utilized for selective visual attention and executive functions (20), the Trail Making Test-A (TMT-A) and Trail Making Test-B (TMT-B) was used for assessing mental flexibility, eye tracking and motor speed (21) and finally Turkish version of the Phonemic Verbal Fluency Test was used to measure the verbal fluency (22, 23).

2.2.3. Measurement of Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Layer Thickness

OCT was measured by a qualified ophthalmologist who was blind to the participants on the same day of cognitive evaluation. For RNFL analysis, the optic nerve head (ONH) protocol of RTVue (Optovue Inc., Foremont, CA, USA) was used. The software automatically defines the optic cup as the intersection of the inner nerve head boundary and a parallel line 150µm above the joining line of the retinal pigment epithelium tips. The RNFL thickness map was generated from RNFL thicknesses measured around an area of 3.45 mm in diameter around the disc center. Mean, superior, inferior, temporal, and nasal hemisphere RNFL thicknesses were provided. Macular parameters were obtained using the GCL protocol of RTVue (Optovue Inc., Foremont, CA, USA). The GCL thickness was measured from the internal limiting membrane to the inner plexiform layer boundary. The following GCL parameters are provided: average, superior, and inferior thickness. The global loss volume (GLV), representing the average GCL loss over the entire GCL map, and the focal loss volume (FLV), representing the local GCL loss using a pattern deviation map to correct for overall absolute changes, were also computed.

2.3. Statistical Analysis

All statistical analyses were conducted using SPSS Version 22.0. We utilized the Chi-square test to compare groups of categorical variables. Comparisons of patients and healthy controls for the continuous variables were undertaken using

Mann-Whitney U tests. Spearman-Brown correlation analysis was used to examine interrelations among continuous variables. For all analyses, the significance was defined as p<.05.

3. RESULTS

We presented the sociodemographic characteristics of patients and healthy controls in Table 1. Group comparisons revealed no difference between groups regarding age, gender, education level, monthly income, and health habits such as packs of cigarettes smoked per day. The only group differences were in marital status (χ^2= 15.25, *p*<.001), current working (χ^2=27.69, *p*<.001), and occupation status (χ^2=14.63, *p*<.001). The patients were mostly single (89.7%), unemployed (86.2%), and did not have any occupation (55.2%).

We presented the clinical characteristics (i.e., PANSS scores, age at the onset of the illness, duration of the disease, the number of hospitalizations, years past the latest hospitalization, the use of clozapine treatment and the presence of psychosis in the family) of the patients with schizophrenia diagnosis at Table 2.

Table 1. *Sociodemographic characteristics of groups*

	Patient Group (n = 29)		Healthy Controls (n= 13)		Group Comparisons	
	Mean	Std. Deviation	Mean	Std. Deviation	Mann-Whitney U Test	*p*
Age	33.83	9.13	32.23	8.04	171.50	.64
Monthly income (Turkish Liras)	2904.14	456.46	3076.92	202.91	119.50	.06
Packs of cigarette smoked	.62	.66	.96	1.01	156.00	.34
	f	%	f	%	Chi-Square Test	
Gender						
Females	6	20.7%	4	30.8%	.50	.70
Males	23	79.3%	9	69.2%		
Marital status						
Single	26	89.7%	4	30.8%	**15.25**	**<.001**
Married	3	10.3%	9	69.2%		
Education						
Primary school	3	10.4%	4	30.8%		
Secondary school	5	17.2%	4	30.8%	4.69	.20
High school	13	44.8%	3	23.0%		
University/college	8	27.6%	2	15.4%		
Current working status						
Working	4	13.8%	13	100%	**27.69**	**<.001**
Unemployed	25	86.2%	0	0%		
Occupation						
None	16	55.2%	0	0%	**14.63**	**<.001**
Blue collar	6	20.7%	10	76.9%		
White collar	7	24.1%	3	23.1%		

***p<.01. ***p<.001.*

Table 2. *Clinical characteristics of the patient group (n= 29)*

	Mean	Std. Deviation
PANSS Positive Symptoms	16.90	6.78
PANSS Negative Symptoms	22.38	7.64
PANSS General Psychopathology	33.48	11.60
PANSS Total	72.76	23.19
Age at the onset of the illness (years)	21.97	6.59
Duration of the illness (years)	11.63	7.57
Number of hospitalizations	2.55	2.50
Latest hospitalization (years past)	4.9130	2.83
	f	%
Use of clozapine treatment	24	57.1%
Presence of psychosis in family	12	28.6%

PANSS: Positive and Negative Syndrome Scale for Schizophrenia

Table 3. *Comparison of healthy controls and the patient group regarding neuropsychological test scores*

Neuropsychological tests	Healthy controls (n=13)		Patient group (n=29)		Mann-Whitney U	*p*
	Mean Rank	Sum of Ranks	Mean Rank	Sum of Ranks		
TMT-total score	26.19	340.50	19.40	562.50	127.50	.10
TMT-A duration	16.04	208.50	23.30	652.50	117.50	.07
TMT-A error	19.50	253.50	21.70	607.50	162.50	.23
TMT-B duration	16.19	210.50	19.07	419.50	119.50	.42
TMT-B error	16.12	209.50	17.58	351.50	118.50	.63
Digit span – forward	19.00	247.00	22.62	656.00	156.00	.36
Digit span – backward	22.69	295.00	20.97	608.00	173.00	.66
Verbal Fluency Test score	27.92	363.00	18.62	540.00	**105.00**	**.02**
Verbal Fluency Test-perseveration	22.77	296.00	20.93	607.00	172.00	.67
Verbal Fluency Test – out of category	19.00	247.00	22.62	656.00	156.00	.39
Verbal Fluency Test – special names	22.81	296.50	20.91	606.50	171.50	.65
STROOP – reading duration	13.58	176.50	25.05	726.50	**85.50**	**.004**
STROOP – reading correction	17.85	232.00	23.14	671.00	141.00	.20
STROOP – response duration	17.46	227.00	21.27	553.00	136.00	.34
STROOP – response error	19.69	256.00	20.15	524.00	165.00	.92
STROOP-response correction	24.38	317.00	17.81	463.00	112.00	.09
STROOP – duration difference	22.04	286.50	18.98	493.50	142.50	.44

**p<.05. **p<.01. TMT: Trail Making Test*

Table 4. *Comparison of patients and healthy controls in terms of retinal nerve fiber layers (RNFL) and ganglion cell layers (GCL)*

	Healthy control (n=9)		Patient group (n=24)		
Retinal Nerve Fiber Layers	Mean Rank	Sum of Ranks	Mean Rank	Sum of Ranks	Mann-Whitney U
Right RNFL mean	19.00	171.00	16.25	390.00	90.00
Left RNFL mean	16.50	148.50	17.19	412.50	103.50
Right RNFL superior	16.72	150.50	17.10	410.50	105.50
Left RNFL superior	17.78	160.00	16.71	401.00	101.00
Right RNFL nasal	18.44	166.00	16.46	395.00	95.00
Left RNFL nasal	14.83	133.50	17.81	427.50	88.50
Right RNFL inferior	20.06	180.50	15.85	380.50	80.50
Left RNFL inferior	15.78	142.00	17.46	419.00	97.00
Right RNFL temporal	19.72	177.50	15.98	383.50	83.50
Left RNFL temporal	16.83	151.50	17.06	409.50	106.50
Ganglion Cell Layers	Mean Rank	Sum of Ranks	Mean Rank	Sum of Ranks	Mann-Whitney U
Right GCL total	19.00	171.00	15.52	357.00	81.00
Left GCL total	21.33	192.00	14.61	336.00	60.00
Right GCL superior	18.11	163.00	15.87	365.00	89.00
Left GCL superior	21.67	195.00	14.48	333.00	57.00
Right GCL inferior	20.56	185.00	14.91	343.00	67.00
Left GCL inferior	20.22	182.00	15.04	346.00	70.00

Note. All Mann Whitney U tests are insignificant at an alpha level of .05.
RNFL: retinal nerve fiber layer GCL: ganglion cell layer

Table 5. *Results of Spearman-Brown correlations among the scores of neuropsychological tests and cell layers for patients (n=24)*

	right_ RNFL_mean	left_ RNFL_mean	right_ RNFL_ superior	left_ RNFL_ superior	right_ RNFL_ nasal	left_ RNFL_ nasal	right_ RNFL_ inferior	left_ RNFL_ inferior	right_ RNFL_ temporal	left_ RNFL_ temporal	right_ GCL_ total	left_ GCL_ total	right_ GCL_ superior	left_ GCL_ superior	right_ GCL_ inferior	left_ GCL_ inferior
TMT-total score	.06	-.08	.06	-.033	.347	.087	.201	.217	-.344	-.176	-.182	-.168	-.268	-.206	-.227	-.133
TMT-A duration	-.12	.12	-.17	.128	-.279	.186	-.164	-.044	.100	.130	-.015	.128	.051	.150	.039	.093
TMT-A error	**.41***	.27	.24	.269	-.052	-.229	.298	.121	**.459***	**.431***	.099	.048	.123	-.018	.026	.022
TMT-B duration	-.09	.03	.06	.100	-.243	.068	-.127	-.123	-.010	-.114	.120	.106	.233	.139	.133	.044
TMT-B error	-.03	-.35	.01	-.156	-.103	-.105	-.053	-.241	-.095	-.265	-.061	-.310	.122	-.229	-.168	-.417
Digit span-forward	-.01	-.23	-.04	-.252	.063	-.229	.111	.060	-.134	-.004	-.127	-.101	-.228	-.147	-.141	-.035
Digit span – backward	-.21	-.25	-.16	-.383	.249	-.082	.078	.032	-.343	-.159	.050	-.096	-.047	-.103	.037	-.050
Verbal Fluency Test score	-.13	-.39	-.08	**-.422***	.251	-.277	.048	-.001	-.351	-.141	-.156	-.299	-.230	-.288	-.144	-.264
Verbal Fluency Test – perseveration	.21	.28	.17	.086	.104	-.030	.294	.309	.022	.139	-.099	-.010	-.085	-.071	-.041	-.021
Verbal Fluency Test – out of category	.11	.19	.10	.222	-.123	.168	-.053	-.120	.318	.258	.242	.241	.318	.261	.229	.173
Verbal Fluency Test – special names	-.10	-.11	.01	-.101	.395	.304	-.066	-.081	**-.427***	**-.459***	-.174	-.124	-.141	-.132	-.085	-.090
STROOP – reading duration	.14	.32	.32	.277	-.216	.231	-.074	.135	.154	.066	.278	.306	.351	.296	.273	.238
STROOP – reading correction	.19	.29	.11	.375	-.143	.404	-.001	.087	.304	-.011	-.052	-.079	.069	-.052	-.072	-.121
STROOP – response duration	**.55****	**.50***	**.51***	**.461***	.035	.350	.310	.204	**.434***	.150	**.646****	.404	**.658****	.397	**.596****	.354
STROOP – response error	.29	.16	.15	.268	.065	.284	.052	-.146	**.430***	-.010	.257	.128	.390	.166	.177	.050
STROOP-response correction	.25	.25	.12	.35	.091	.307	-.068	-.089	.284	.247	.213	.329	.323	.358	.138	.243
STROOP – duration difference	.28	.11	.04	.14	-.073	.137	.413	-.001	.370	.079	.276	.007	.237	-.022	.249	.003

**p<.05. **p<.01. RNFL: retinal nerve fiber layer GCL: ganglion cell layer TMT: Trail Making Test*

Table 3 compared healthy controls and the patient group on neuropsychological test scores. Patients (Mean Rank = 18.62) had significantly lower verbal fluency indicated by verbal fluency total score than the healthy controls (Mean Rank = 27.92), Mann-Whitney U = 105.00, p=.02. Patients' reading duration in STROOP test (Mean Rank = 25.05) was significantly higher than controls (Mean Rank = 13.58), Mann-Whitney U = 85.50, p =.004. Patients did not significantly differ from healthy controls regarding other scores on neuropsychological tests.

We compared the patient group's and healthy controls' retinal nerve fiber layers (RNFL) and ganglion cell layers (GCL) thickness. As seen in Table 4, groups did not significantly differ regarding RNFL variables or the values on GCL. We further assessed the relationship between cognitive task scores and RNFL and GCL for all participants. We presented the correlations among nerve layers and scores of the neuropsychological tests for the patient group in Table 5.

3.1. Correlations Between the Scores of Neuropsychological Tests and OCT Measures for All Respondents

Spearman Brown correlational analyses on all participants revealed positive relations between TMT total scores and right RNFL nasal values (ρ = .387, p <.05); errors from TMT-A and right RNFL temporal (ρ = .373, p <.05) as well as left RNFL temporal values (ρ = .362, p <.05). For all participants, verbal fluency test perseveration score was positively correlated with left RNFL on average (ρ = .370, p <.05) and left RNFL inferior (ρ = .401, p <.05). In contrast, verbal fluency test special names score was negatively correlated with left RNFL temporal (ρ = – .355, p <.05). STROOP response duration positively correlated with right RNFL on average (ρ = .361, p <.05), left RNFL on average (ρ = .421, p <.05), right RNFL superior (ρ = .410, p <.05) and left RNFL superior values (ρ = .424, p <.05). STROOP reading correction was positively related to left RNFL nasal thickness (ρ = .409, p <.05) for all participants. In terms of the correlation between cognitive task scores and GCLs, STROOP response duration positively correlated with right GCL total (ρ = .420, p <.05), right GCL superior (ρ = .381, p <.05) and right GCL inferior (ρ = .377, p <.05). Finally, STROOP reading correction positively correlated with left GCL superior (ρ = .363, p <.05).

3.2. Correlations Between the Scores of Neuropsychological Tests and OCT Measures for Patients

For the patient group, TMT-A error score positively correlated with right RNFL on average (ρ = .414, p <.05), right RNFL temporal (ρ = .459, p <.05), and left RNFL temporal (ρ = .431, p <.05) thickness. The verbal fluency test score negatively correlated with left RNFL superior (ρ = – .422, p <.05), while the verbal fluency test special names score negatively correlated with right RNFL temporal (ρ = – .427, p <.05) and left RNFL temporal (ρ = – .459, p <.05) values. STROOP response duration positively correlated with right RNFL on average (ρ = .551, p <.05), left RNFL on average (ρ = .498, p <.05), right RNFL superior (ρ = .507, p <.05), left RNFL superior (ρ = .461, p <.05) and right RNFL temporal values (ρ = .434, p <.05). STROOP response error was also positively correlated with right RNFL temporal thickness (ρ = .430, p <.05). STROOP response duration was positively correlated with right GCL total (ρ = .646, p <.01), right GCL superior (ρ = .658, p <.01) and right GCL inferior (ρ = .596, p <.01) thickness.

Table 6. *Correlations between clinical indicators of schizophrenia and retinal and ganglion cell layers*

	PANSS-p	PANSS-n	PANSS-g	Age of onset	Duration of illness	Numbers of hospitalizations	International Consensus Study of Antipsychotic Dosing	Chlorpromazine equivalence (mg)
right RNFL mean	**.501***	**.442***	**.485***	-0.173	-0.115	0	.033	-.031
left RNFL mean	**.460***	0.379	**.483***	-0.236	0.123	0.052	.082	.086
right RNFL superior	0.288	0.268	0.217	-0.041	0.081	0.13	-.217	-.153
left RNFL superior	**.555****	0.332	**.537****	-0.305	0.232	-0.004	-.171	-.137
right RNFL nasal	0.051	-0.007	0.071	-0.051	-0.389	-0.139	-.128	-.223
left RNFL nasal	0.115	-0.023	0.091	-0.276	0.119	-0.026	.084	.115
right RNFL inferior	0.188	0.337	0.139	-0.025	-0.244	0.011	.195	.128
left RNFL inferior	0.182	0.116	0.118	0.016	-0.138	0.044	.352	.375
right RNFL temporal	**.529****	**.532****	**.451***	-0.074	0.051	-0.008	.185	.093
left RNFL temporal	**.429***	0.324	**.515***	-0.187	0.074	-0.052	.055	-.043
right GCL total	0.202	0.282	0.271	-0.068	0.178	-0.157	-.264	-.312
left GCL total	0.278	0.201	0.409	-0.251	0.197	-0.215	-.322	-.337
right GCL superior	0.224	0.401	0.296	-0.055	0.103	-0.094	-.268	-.306
left GCL superior	0.3	0.195	**.461***	-0.314	0.191	-0.239	-.335	-.365
right GCL inferior	0.128	0.233	0.138	0.088	0.154	-0.105	-.122	-.197
left GCL inferior	0.223	0.143	0.307	-0.139	0.132	-0.251	-.242	-.274

**p<.05. **p<.01. PANSS: positive and negative symptom scale PANSS-p: PANSS positive symptom score PANSS-n: PANSS negative symptom score PANSS-g: PANSS general psychopathology symptom score RNFL: retinal nerve fiber layer GCL: ganglion cell layer*

3.3. Correlations Between the Clinical Indicators of Disease Severity and OCT Measures

Finally, we assessed the relationship between clinical features with RNFL and GCL thickness. We did not find any significant correlation between OCT measures and age of onset, duration of schizophrenia, number of hospitalizations, or the dosage of current antipsychotic use. PANSS positive (PANSS-p) scores were correlated with right and left average RNFL thickness, left RNFL superior, and right and left RNFL temporal regions. PANSS negative symptom scores (PANSS-n) were significantly correlated with the right RNFL average and temporal areas. General psychopathology scores (PANSS-g) positively correlated with right RNFL mean, left RNFL average, left RNFL superior, and right RNFL temporal values. Finally, only a significant correlation was detected between PANSS-g and left GCL superior thickness. The details of the correlations are presented in Table 6.

4. DISCUSSION

This study examined the differences in OCT findings between the patients with schizophrenia and healthy participants and explored the relationships between various cognitive functions and retinal structural alterations in patients. Our initial hypothesis in this study was patients would have thinner RNFLs and GCLs than healthy controls. Second, thinning of retinal nerve and ganglion cell layers due to possible neurodegeneration would correlate with the loss of cognitive functions and more clinical severity in patients with schizophrenia. Contrary to our hypothesis, OCT measures did not differ between patients and healthy controls. Regarding cognitive correlations, only verbal fluency task scores were correlated with thinner left RNFL superior, right RNFL temporal, and left RNFL temporal values. Moreover, we detected several positive correlations between poorer cognitive performance and layer thicknesses in several retinal regions. In terms of disease-related clinical parameters, interestingly, there were positive correlations between PANSS scores and mean, superior, and temporal RNFL thicknesses.

The demonstration of thinning of the RNFLs and GCLs in early OCT studies prompted researchers to pursue new research to find a new biomarker in schizophrenia (24, 25). In addition to various studies showing thinning of the peripapillary retinal nerve layers, (13) there is a considerable number of studies that did not detect significant atrophy in RNFLs in patients with schizophrenia (16, 26, 27). Studies suggest that longer duration of the illness (28), comorbid medical conditions such as hypertension or diabetes (27), and the presence of recent illness episodes (29) affect the thinning of RNFL and GCL or macular thicknesses. Age, body mass index, and metabolic syndrome were also reported as confounding factors on the relationship between schizophrenia and RNFL thickness (26). Our analysis also did not determine any significant difference in RNFL or GCLs between patients and healthy controls. This negative finding may be related with non-psychiatric medical conditions of the participants which we did not assess in our study.

The association of cognitive functioning with RNFL thickness in healthy individuals was reported in a previous study. The authors noted that better cognitive performance was related to a thicker RNFL in only young individuals, but this association diminished in older age groups (30). In schizophrenia, a few studies assessed the cognitive correlations of retinal findings (17, 31, 32). One study found that lower scores of immediate memory and visuospatial functions of the RBANS (Repeatable Battery for the Assessment of Neuropsychological Status) were correlated with a decline in RNFL thickness. In contrast, not found any correlation between language, attention, delayed memory, and RNFL (31). The other study of the same group reported a significant correlation between RNFL thickness thinning and lower scores on the Stroop Color Word reading test (32). Finally, a recent study examined the correlations between executive functioning, attention, memory/learning and OCT results. Thinning of the right inner plexiform layer and left macula were associated with worse executive functioning and attention. However, they did not find a significant correlation between cognitive task scores and the thinning of RNFL, GCL, and choroid (17). Our study found no significant correlation between deterioration in executive functions, attention, working memory, and thinning of the RNFL or GCL layers. Interestingly, we even found a relationship between the poorer scores in verbal fluency, STROOP response duration, response error, and thicker RNFL and GCL. When all the results are put together, the results seem inconsistent and complex.

Finally, concerning the correlation between clinical severity and OCT measures, we did not find any significant relationship between RNFL, GCL thinning, symptom severity, or other disease-related severity indicators. This finding is consistent with many studies in the literature that did not find a relationship between disease severity and OCT findings (17, 25, 28, 33, 34).

Several limitations should be acknowledged. First, our sample size is relatively small; given the limited power, non-significant results should be approached with caution. Second, according to the total PANSS scores, our sample consisting of patients with moderate illness severity, may restrict the generalizability of our results. Third, we did not assess the confounding factors such as age, smoking, other medical comorbidities, and cardiometabolic factors. Finally, however, we evaluated the current dosage of antipsychotic drugs cross-sectionally; we cannot exclude the possible retinal effects of cumulative antipsychotic use.

5. CONCLUSION

RNFL and GCL thicknesses did not differ between schizophrenia patients and healthy controls, and we did not detect any significant correlation between retinal thinning and cognitive impairment as a result of our cognitive evaluation. Although our results support negative studies

of OCT in schizophrenia, prospective studies conducted in larger samples are required to show whether OCT can be a prognostic marker. In future studies, besides cognitive tasks showing instant performance, evaluating functionality and investigating whether the deterioration in these areas is correlated with the thinning in repetitive OCT measurements will provide more accurate information.

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Acquisition of data for the study: CŞÇ, MD, EBÇ, SAT
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