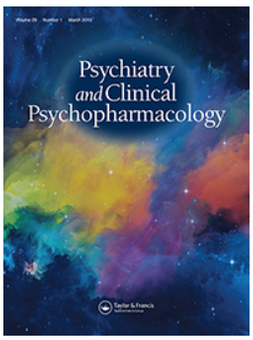

Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

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To cite this article: Pinar Topcu-Yilmaz, Memduha Aydin & Bilge Cetin Ilhan (2019) Evaluation of retinal nerve fiber layer, macular, and choroidal thickness in schizophrenia: spectral optic coherence tomography findings, Psychiatry and Clinical Psychopharmacology, 29:1, 28-33, DOI: 10.1080/24750573.2018.1426693

To link to this article: https://doi.org/10.1080/24750573.2018.1426693

Published online: 29 Jan 2018.

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY
2019, VOL. 29, NO. 1, 28–33
https://doi.org/10.1080/24750573.2018.1426693

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Evaluation of retinal nerve fiber layer, macular, and choroidal thickness in schizophrenia: spectral optic coherence tomography findings

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ABSTRACT

OBJECTIVES: The study was performed to evaluate the retinal nerve fiber layer (RNFL), macular, and subfoveal choroidal thickness (SFCT) in patients with schizophrenia and healthy controls using spectral domain optical coherence tomography (SD-OCT).

METHODS: Fifty-nine schizophrenic patients and 36 age- and sex-matched healthy volunteers were enrolled in this cross-sectional clinical study. The RNFL, macular, and SFCT thickness measurements obtained by SD-OCT were compared between the groups.

RESULTS: The mean age of 59 patients included in this study was 34.64 years and the mean age of 36 healthy controls was 32.08 years, mean illness duration was 10.33 years, mean total Positive and Negative Symptom Scale (PANSS) score was 75.18, and mean CGI-S score was 3.88. Macular thickness in the superior inner (350.97 ± 16.51 vs. 341.81 ± 16.35), nasal inner (348.97 ± 17.53 vs. 340.25 ± 17.55), inferior inner (345.5 ± 17.59 vs. 335.47 ± 16.92), temporal inner (333.28 ± 17.96 vs. 321.97 ± 19.96), and temporal outer (289.14 ± 14.10 vs. 281.29 ± 15.31) segments were significantly decreased in schizophrenic patients. However; RNFL thickness and choroidal thickness (CT) measurements between the two groups were similar. No significant correlation was found between illness duration, PANSS score, CGI-S score and RNFL thickness and macular thickness measurements. There was a weak negative correlation between disease duration and CT.

CONCLUSIONS: The findings from this study suggest that macular thickness measurements are reduced in schizophrenic patients but do not indicate any significant change in RNFL or choroids. Further studies are needed to determine the potential application of optical coherence tomography as a tool for the diagnosis and monitoring the progression of this disease.

ARTICLE HISTORY
Received 17 November 2017
Accepted 8 January 2018

KEYWORDS
Choroidal thickness; macular thickness; optical coherence tomography; retinal nerve fiber layer thickness; schizophrenia

Introduction

Schizophrenia is a progressive, chronic, and disabling mental disorder characterized by positive, negative, and cognitive symptoms that affect almost all aspects of mental activity, including perception, attention, memory, and emotion [1]. The etiology and fundamental pathophysiology of schizophrenia remain unclear, but a large body of evidence suggests that many factors, including genetic, environmental, neurodevelopmental, and neurodegenerative factors make a contribution to pathophysiological processes [2]. Increasingly advanced neuroimaging technologies and neuropathological methods are used frequently in various types of studies to support the neurodevelopmental and neurodegenerative hypothesis of schizophrenia [3,4].

The structural brain abnormalities in schizophrenia involve the gray matter volume deficits, white matter abnormalities, and ventricular enlargement observed in these neuroimaging studies support the neurodevelopmental hypothesis of schizophrenia [5–8]. Numerous neuropathological and neuroimaging studies of schizophrenia representing the effect of the disease on the brain after it has begun often support neurodegenerative hypothesis of schizophrenia [9]. Decreases in the total brain volume as well as decreases in the numbers and functions of neurons have been demonstrated not only in chronic schizophrenia patients but also in the first episode and prodromal stage patients [10,11]. Findings from neuroimaging studies of patients with schizophrenia also support that neurodegeneration starts at the earliest stages of schizophrenia [5,12–14].

Another hypothesis called the progressive neurodevelopmental model has been proposed to provide a unifying hypothesis that conceptualizes schizophrenia neither entirely neurodevelopmental nor solely neurodegenerative [9]. It may be said that schizophrenia requires more neurobiological explanations supporting these complementary theories.

The retina is anatomically and developmentally an extension of the central nervous system, and the retina

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and the brain are connected by the optic nerve [15]. Thus, the retina and its subcortical projections have become a crucial site of research for schizophrenia in the last decade. Visual evoked potential studies demonstrated a selective dysfunction of the magnocellular pathway [16]. Electroretinogram studies have shown that the cone a-wave amplitude was decreased indicating a photoreceptor dysfunction in the acute phase of psychosis [17,18].

Over the past years, researchers have extensively focused on the role of functional and structural neuroimaging in schizophrenia in order to understand the underlying neurobiology and develop reliable biomarkers for diagnosis [19]. As one of these, optical coherence tomography (OCT) is a relatively new, contactless, non-invasive imaging method that permits *in vivo* visualization of the optic nerve and can easily provide high resolution, cross-sectional images of the retina and choroid [20]. While OCT is primarily used for the follow-up of ocular pathologies, it has also gained importance for the detection of retinal and choroidal changes that might be valuable as a biomarker of several neurodegenerative diseases [21].

The diseases classically described as neurodegenerative are Alzheimer's disease, Huntington's disease, Parkinson's disease, and Multiple Sclerosis. Several studies have reported retinal nerve fiber layer (RNFL) thinning in Alzheimer's disease, mild cognitive impairment, Parkinson's disease, and Multiple Sclerosis [22–25]. However; very few studies have investigated the RNFL and macular thickness changes in psychiatric disorders as schizophrenia and depression [4, 26–30].

It was concluded that peripapillary RNFL thinning is associated with neuronal cell loss and axonal loss [31]. The studies of OCT in patients with schizophrenia demonstrated a decrease in the RNFL thickness which can be explained by neuronal cell and axonal loss as a process of neurodegeneration. The RNFL is a beneficial structure for detecting the severity and duration of the disorder, and it has been suggested that OCT, measuring the RNFL thickness, may be used as a diagnostic tool in schizophrenia.

Data from clinical, pathological, and neuroimaging studies have also revealed evidence of vascular involvement in schizophrenia [32–34]. Recently, Meier et al. [35] have shown that wider retinal venules were a distinguishing feature of schizophrenia. This finding was also supported by a study on twins that found an association with wider retinal venules and psychosis symptoms [36]. Choroid is the other vascular tissue supplying more than 70% of blood flow in the eye and can also be affected by microvascular changes in schizophrenia.

The purpose of this study was to evaluate the RNFL, macular, and subfoveal choroidal thickness (SFCT) in patients with schizophrenia and to compare them with healthy controls. We also aimed to investigate the associations between OCT measurements and clinical parameters of the schizophrenic patients.

Methods

Participants

A total of 65 patients who had been consecutively admitted to the psychiatry inpatient clinic of Konya Training and Research Hospital with the diagnosis of schizophrenia and fulfilled DSM-IV criteria between December 2014 and May 2015 were included in this cross-sectional, observational study [37]. Six patients were excluded for clinical reasons. Four patients were excluded due to refractive errors with a spherical equivalent greater than 2.00 D, one patient was excluded due to cataract that precluded OCT examination and one patient was excluded due to strabismic amblyopia that could affect OCT results. The final sample in the study included 59 patients with schizophrenia. The control group consisted of 37 age- and gender-matched healthy volunteers. The study protocol was approved by the Institutional Review Board of Selcuk University Faculty of Medicine, Konya and adhered to the tenets of the Declaration of Helsinki (18 November 2014; 2014/305). Informed consent was obtained from all subjects prior to their participation in the study. Criteria for the exclusion of a subject from the study were as follows: (1) A history of an ophthalmological, neurological, or systemic condition that could affect the RNFL or macula (such as amblyopia, glaucoma, age-related macular degeneration, diabetes mellitus, hypertension, optic neuropathy, ocular trauma, ocular surgery, intraocular pressure (IOP) greater than 21 mmHg, etc.), (2) refractive errors greater than ± 2.0 diopters of spherical equivalence, and (3) media opacities that preclude OCT examination.

Measures

Sociodemographic and Clinical Data Form: Semi-structured sociodemographic and clinical data form was developed by the researchers of the study. Patients were interviewed face-to-face by psychiatrists who were experienced in working with schizophrenic patients on basis of this sociodemographic and clinical data form. Medical records, including patient sociodemographic and clinical variables, and reports from relatives and/or care-givers are also used as information sources.

The PANSS: PANSS is a semi-structured interview scale involving 30 items and a seven-point severity rating. Seven parameters are included in the positive syndrome subscale, 7 parameters are included in the negative syndrome subscale, and the remaining 16 parameters are included in the general psychopathology subscale [38]. The reliability and validity of the

Turkish-language version of the scale were established by Kostakoglu et al. [39].

Clinical Global Impression Scale: Global severity of psychopathology was determined by using the Clinical Global Impression Scale-Severity (CGI-S) [40]. This scale has ratings from 1 (not ill) to 7 (extremely ill).

Procedure

Patients were interviewed face-to-face by psychiatrists who were experienced in working with schizophrenic patients. Those who are clinically partially stable have been directed to ophthalmologic examination after psychiatric interventions within the second week of hospitalization. Lack of aggression/negativism was the most important item taken into consideration before ophthalmologic evaluation. Subjects included in the study underwent a complete ophthalmologic evaluation including retinoscopy, slit lamp biomicroscopy, IOP measurement, fundus examination. Spectral domain optical coherence tomography (SD-OCT) images for the measurement of RNFL, macular, and choroidal thickness (CT) were taken by an experienced technician (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). In order to avoid the diurnal variation in CT, all OCT examinations were performed between 1:00 pm and 2:00 pm. RNFL imaging was performed using circular scans of 3.4 mm diameter at the center of the optic disc. RNFL thickness at six sectors (nasal (N), superonasal (SN), superotemporal (ST), temporal (T), inferotemporal (IT), inferonasal(IN), and global (G) RNFL thickness) were automatically calculated by the SD-OCT device. The macular thickness results were noted for nine subfields as defined by the ETDRS study [Central foveal subfield (CFS), superior inner macula (SIM), superior outer macula (SOM), nasal inner macula (NIM), nasal outer macula (NOM), inferior inner macula (IIM), inferior outer macula (IOM), temporal inner macula (TIM), temporal outer macula (TOM)]. Only well-centered, high-quality images with a signal strength >15 dB were included in the study.

The CT was measured manually from the outer edge of the retinal pigment epithelium to the inner scleral surface at the fovea and at positions 500, 1000, and 1500 μ nasal and temporal to the fovea. Measurements were done by the same ophthalmologist (P.T.Y.) who was masked to the diagnosis of study participants. Images with low image quality resulting in an indiscernible choriosclera border were excluded from the study.

Statistical analyses

Statistical analysis was performed using SPSS ver. 17.0 (Chicago, IL, USA). Only one eye of each subject was included for the analysis. Once the normality of the data was determined via Kolmogorov Smirnov test; Mann–Whitney *U*-test was used to compare the RNFL, macular, and CT values in patients with schizophrenia and healthy volunteers. The categorical variables were analyzed by the Pearson χ^2 test. Spearman's rank correlation analysis tests were used for correlative analyses. Effect sizes (r^2) reported for significant findings for between-group comparisons. For all evaluations, a p-value of less than .05 was considered as statistically significant.

Results

Fifty-nine patients with schizophrenia and 37 healthy volunteers were included in the study. The mean age of schizophrenic patients was 34.64 ± 9.49 and the mean age of healthy controls was 32.08 ± 12.33. There was no statistically significant difference in the mean age ($p = .26$) and gender ($p = .27$) of the two groups. Detailed demographic characteristics of the study groups can be found in Table 1.

The mean total PANSS score was 75.19 ± 20.14 and mean CGI-S score was 3.88 ± 1.22 in the schizophrenia group. Ten patients were treated with typical antipsychotics, 38 patients were treated with atypical antipsychotics and 11 patients were drug naïve on admission.

The mean peripapillary RNFL thickness at all sectors was similar in schizophrenic patients and healthy controls (Table 2). Comparison of the macular thickness between the two groups showed that macular thickness was decreased in schizophrenia patients, and this difference was statistically significant for superior inner (341.81 ± 16.35 vs. 350.97 ± 16.51; $r^2 = 0.063$; $p = .01$), nasal inner (340.25 ± 17.55 vs. 348.97 ± 17.53; $r^2 = 0.09$; $p = .02$), inferior inner (335.47 ± 16.92 vs. 345.5 ± 17.59; $r^2 = 0.140$; $p = .008$), temporal inner (321.97 ± 19.96 vs. 333.28 ± 17.96; $r^2 = 0.145$; $p = .006$), and temporal outer (281.29 ± 15.31 vs.

Table 1. Demographic characteristics of the study population.

	Schizophrenia ($n = 59$)	Control ($n = 37$)	p
Age (years)	34.64 ± 9.49	32.08 ± 12.33	.26
Sex			.27
Male	32 (%54.2)	15 (40.5)	
Female	27 (%45.8)	22 (59.5)	
Duration of illness			
Acute	8 (%13.6)		
Chronic	51 (%86.4)		

Table 2. Comparison of RNFL thickness in schizophrenia and healthy controls.

	Schizophrenia	Control	p
Nasal RNFL thickness	75.37 ± 12.80	74.49 ± 12.55	.74
Superonasal RNFL thickness	104.73 ± 22.33	102.51 ± 17.38	.73
Superotemporal RNFL thickness	135.31 ± 18.95	136.40 ± 16.14	.28
Temporal RNFL thickness	73.64 ± 10.54	74.70 ± 9.63	.62
Inferotemporal RNFL thickness	152.64 ± 16.35	156.22 ± 15.01	.76
Inferonasal RNFL thickness	118.37 ± 23.88	116.73 ± 21.59	.59
Global RNFL thickness	101.32 ± 8.53	101.27 ± 6.98	.97

289.14 ± 14.10; $r^2 = 0.142$; $p = .01$) macular thickness (Table 3). The CT measurements at all measurement points were similar between the study and control groups (Table 4).

No correlation was noted between the RNFL thickness, macular thickness and PANNS score or disease duration. Subfoveal, 500 Nasal, 1500 Nasal, and 500 Temporal CT measurements had a weak negative correlation with disease duration (Table 5).

Discussion

In the present study, we used SD-OCT to evaluate the RNFL, macular, and subfoveal CT in 59 patients with schizophrenia and 37 healthy controls. Our findings suggest that macular thickness measurements are reduced in schizophrenic patients, but showed no differences between patients with schizophrenia and healthy controls in terms of RNFL thickness and CT measurements.

Table 3. Comparison of macular thickness in schizophrenia and healthy controls.

	Schizophrenia	Control	*p*
Central foveal thickness (μm)	265.56 ± 24.83	265.28 ± 21.66	.95
Superior inner macular thickness (μm)	341.81 ± 16.35	350.97 ± 16.51	**.01**
Superior outer macular thickness (μm)	294.22 ± 13.50	298.03 ± 11.44	.15
Nasal inner macular thickness (μm)	340.25 ± 17.55	348.97 ± 17.53	**.02**
Nasal outer macular thickness (μm)	312.63 ± 21.60	320.22 ± 15.73	.05
Inferior inner macular thickness (μm)	335.47 ± 16.92	345.5 ± 17.59	**.008**
Inferior outer macular thickness (μm)	289 ± 14.42	294.19 ± 12.37	.07
Temporal inner macular thickness (μm)	321.97 ± 19.96	333.28 ± 17.96	**.006**
Temporal outer macular thickness (μm)	281.29 ± 15.31	289.14 ± 14.10	**.01**

Note: The significance of bold value indicates $p < .05$.

Table 4. Comparison of CT of schizophrenia patients and healthy controls.

	Schizophrenia	Controls	*p*
Subfoveal CT	341.18 ± 63.42	329.89 ± 69.03	.20
500 nasal CT	322.63 ± 65.05	309.97 ± 71.13	.21
1000 nasal CT	305.92 ± 67.37	294.11 ± 72.19	.27
1500 nasal CT	278.02 ± 66.95	272.94 ± 71	.55
500 temporal CT	325.92 ± 60.39	319.83 ± 67.92	.39
1000 temporal CT	316.16 ± 62.31	309.14 ± 69.92	.40
1500 temporal CT	303.78 ± 66.21	297.83 ± 69.72	.54

Note: CT: choroidal thickness.

Table 5. Correlation between CT and disease duration in schizophrenia.

	Disease duration	
	r	*p*-Value
Subfoveal CT	−0.38	**.006**
500 nasal CT	−0.33	**.02**
1000 nasal CT	−0.26	.07
1500 nasal CT	−0.27	**.05**
500 temporal CT	−0.27	**.05**
1000 temporal CT	−0.26	.07
1500 temporal CT	−0.24	.09

Note: CT: choroidal thickness. The significance of bold value indicates $p < .05$.

While our findings are in line with an earlier study [27], several other groups have reported significant RNFL thinning in schizophrenia [4,26,28–30]. The earliest study investigating the retinal changes in schizophrenia was a short report on 10 patients and found that overall RNFL thickness and nasal RNFL thickness were reduced in the patient group [26]. A larger study by Lee at al. [28] have shown that overall peripapillary RNFL thickness, superior, temporal, and inferior RNFL thickness were significantly reduced in schizophrenia. This reduction was correlated with the duration of illness and was much more significant in patients with longer disease duration. The thinning in RNFL was also confirmed by Yilmaz et al. [30] and Celik et al. [4]. Celik et al. [4] also reported that decreases in specific cell layers (i.e. ganglion cell layer, inner plexiform layer) volumes correlate better with disease severity in schizophrenia patients than RNFL thickness. Recently, Ascaso et al. [29] have evaluated the retinal OCT findings in schizophrenia patients with recent and non-recent illness episode. Interestingly, patients with a recent illness episode (RIE) had similar RNFL thickness with controls and the reduction in RNFL thickness was only significant for patients clinically stable for more than six months. They suggested that the ongoing inflammatory processes during the acute psychotic episodes might also affect the retina, increase its thickness, and mask the RNFL thinning in these patients. As all of our patients were recruited from the inpatient clinic of the Psychiatry Department and were having a recent psychotic episode, the absence of RNFL thinning in our study might be comparable to the lack of significant difference in RNFL thickness of RIE patients and healthy controls in the study by Ascaso et al. [29]. Future longitudinal studies would be helpful to prove the role of inflammation on RNFL changes of schizophrenia patients.

The second parameter investigated in this study was the macular thickness and it was found to be reduced in patients with schizophrenia. This reduction was statistically significant for superior inner, nasal inner, inferior inner, temporal inner, and temporal outer segments. Several other studies have also reported decreased macular thickness in schizophrenia [28,29]. Lee et al. [28] have found a negative correlation between disease duration and macular thickness. However; such an association was lacking in the study by Ascaso et al. [29] and our study.

The association between microvascular abnormalities and schizophrenia has been an interesting research topic since the 1960s [41]. Demonstration of wider retinal venules in individuals with psychotic symptoms or schizophrenia has drawn attention to the possible role of retinal imaging for clarifying the pathophysiology in these patients [35,36,41]. As a highly vascular tissue

supplying oxygen and nutrients to the outer retina, choroid is another candidate for detection of microvascular abnormalities. Recently, several investigators have focused on the choroidal changes in neurodegenerative diseases. Gharbiya et al. [42] and Bayhan et al. [43] have found that CT was significantly reduced in patients with Alzheimer's disease. Choroidal thinning was also reported in Parkinson's disease [44]. Our study was the second study to evaluate the choroidal structure in schizophrenia and was unable find a significant difference in the CT of patients with schizophrenia and healthy controls. This was consistent with the findings of Celik et al. [4]. Interestingly, our results showed a weak negative correlation between CT and disease duration, but this result should be confirmed by further studies before drawing a conclusion.

We recognized several limitations to the present study. The lack of confirmation of diagnoses and schizophrenia subtypes with a structured clinical interview such as SCID-I is among the major limitations of our study. The control subjects were not evaluated with a clinical interview also. The heterogeneity of patients in terms of disease progression (i.e. acute/ chronic) and in terms of treatments received (i.e. type of antipsychotics used for treatment, total dose of antipsychotics received since disease onset in chlorpromazine equivalents, etc.) is another limitation that make it difficult to generalize the results and to make comparisons between different subgroups. It was speculated that longer periods of the recent depressive episode cause more retinal atrophy by Yıldız et al. [45]. Recent depressive episode of patients is another issue that should be considered while evaluating retinal degeneration due to schizophrenia. The lack of information about depressive episodes of our patient group is one of the limitations. Last of all, evaluating the PANSS scores as total may cause ignorance of the specific effect of some symptoms. Relative importance of specific symptoms (i.e. visual hallucinations) was pointed in a recent review study by Bernardin et al. [46] Assessment of positive syndrome subscale, negative syndrome subscale, and general psychopathology subscale of PANSS separately could help confirm the hypothesis that suggests correlations between symptom severity and retinal degeneration in schizophrenia patients.

In conclusion, this study confirmed that macular thickness was reduced in patients with schizophrenia. Though most of the previous reports found thinner RNFL thickness measurements in schizophrenia, we were unable to find such a change in our study population. Longitudinal studies with a long-term follow-up may be useful to establish the role of OCT in the follow-up of these patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The study protocol was approved by the Institutional Review Board of Selcuk University Faculty of Medicine, Konya, TURKEY.

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