# A structural and functional study of the retina in patients with schizophrenia

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***Purpose:*** *To examine the relationship between retinal structural parameters and visual perception function in patients with schizophrenia.*

***Material and Methods:*** *Twenty-four subjects (48 eyes) were included in the study. Group 1 (the schizophrenia group) comprised 11 patients with paranoid schizophrenia and one with schizotypical personality disorder, and Group 2 (the control group) comprised 12 mentally healthy subjects. Group 1 was subdivided into Subgroup A (disease duration of > 5 years) Subgroup B (disease duration of < 5 years). Subjects underwent a routine eye examination, assessment of contrast sensitivity threshold using Ergotest 3.0 software, and optical coherence tomography (OCT) of the retina using a Topcon 3D OCT 2000 apparatus in 3D Macula, Radial Macula and 3D Disc modes.*

***Results:*** *Compared to the control group, the patients with schizophrenia exhibited significantly (p < 0.05) lower contrast sensitivity threshold values at high spatial frequencies. The contrast sensitivity threshold at high spatial frequencies was negatively correlated with disease duration (p=0.046, r=-0.585). OCT-based macular parameters and the diameter of the foveola in these patients tended to increase compared with controls, but only differences in the macular volume (p = 0.035), superior inner retinal thickness (p = 0.022) and nasal inner retinal thickness (p = 0.003) for both eyes were significant.*

***Conclusion:*** *Our findings in patients with schizophrenia confirm previously reported evidence of dysfunction of the parvocellular visual channels in the early disease stages. In addition, they confirm the hypothesis that there is an association of an acute psychotic episode with neuroinflammation and subclinical retinal edema in the macula.*

## Introduction

The changes in the visual system in schizophrenia were noted by Kraepelin and Bleuler more than a hundred years ago [1]. Shamshinova [2] and Goldovskaia [3] systematically studied basic visual functions and effects of psychotropic drugs on these functions in patients with schizophrenia.

Psychophysical and electrophysiological studies have demonstrated evidence of impaired visual perception levels in each of the hierarchical levels of the visual system, from the retina to the anterior areas of the visual cortex. This is manifested by the altered balance between magnocellular (M pathway) and parvocellular visual channels (P pathway) which in turn is expressed by changes in retinal contrast sensitivity and visual evoked potentials [4,5]. Given that central vision function is performed mostly by small receptive fields in the macular region which form parvocellular visual channels, obtaining information on the structure of the region in patients with schizophrenia may contribute to establishing the structural and functional relationship in the macula of these patients.

Optical coherence tomography (OCT) enables studying the ultrastructure of the retina and optic disc in vivo (Fig. 1) at the histological level. OCT studies in patients with Alzheimer's disease [6], multiple sclerosis [7-9], and senile cerebral atrophy [10] have demonstrated evidence of thinning of the peripapillary retinal nerve fiber layer (RNFL) that consists mostly of ganglia axons. In addition, an OCT study by Tiganov et al [11] reported on thinning of the macular ganglion cell complex in Alzheimer's disease. Moreover, RNFL thinning has been

demonstrated in dopamine-associated disorders such as Parkinson's [12]. An OCT study by Moiseenko [13] has established the relationship between the size of the foveola and resolution of the eye and the effects of this size both on early VEP latencies and cognitive processes in reading. It has been hypothesized that the larger the foveola, the more foveal receptive fields are activated, which consequently stimulates the parvocellular visual system that enables high-frequency data transfer. Therefore, OCT studies of the retinal structures involved in the formation of the magnocellular and parvocellular visual channels may be important in patients with schizophrenia.

**The purpose** of the study was to examine the relationship between retinal structural parameters and visual perception function in patients with schizophrenia.

### Material and Methods

Group 1 (the study group) comprised 11 patients with paranoid schizophrenia and one patient with schizotypical personality disorder, with a mean disease duration of $8.5\pm5.4$ years. Of these, 10 were in-patients with acute disease, and two were in remission for more than a year. All patients of this group were administered antipsychotic medications. Exclusion criteria were (1) high myopia with secondary changes in the fundus, (2) any macular disorder, or (3) optic neuropathy. Group 2 (the control group) was composed of mentally normal individuals. The two groups were matched in age and gender.

At baseline, subjects underwent a preliminary eye examination that included autorefractometry, pneumotonometry, IOL Master axial length measurements, visual acuity assessment using digital optotypes, and the Mollon-Reffin minimalist color vision test. Thereafter, they underwent assessment of retinal contrast sensitivity threshold using Ergotest 3.0 software with gradual increases in spatial frequency of presented Gabor lattice from 0.3 to 9.0 cycles per degree of visual angle and in contrast from 0 to 1. Then patients had biomicroscopy of the anterior and posterior eye, and ophthalmoscopy using a 78D lens. Finally, the fundus was examined using Topcon 3D OCT 2000 in 3D Macula [6.0 x 6.0 mm – 512 x 128], Radial Macula [6.0 mm – 102 x 12] and 3D Disc modes. The foveal diameter was calculated as the mean of manually measured distance between the margins of the inner plexiform layer for six scans (0-, 30-, 60-, 90-, 120-, and 150-degree scans) in Radial Macula mode. The following optic disc parameters were assessed: optic disc area (Disc Area), cup-to-disc (C/D) Area Ratio, neuroretinal rim area (Rim Area) and total RNFL thickness (RNFL Total).

Statistical analyses were conducted using Microsoft Excel and IBM SPSS 24. Descriptive statistics was performed in the form of mean and standard deviation for interval variables. Mann-Whitney test was used for independent sample comparisons. Single-factor analysis of variance (ANOVA) was used to detect significant differences between the groups. The Pearson test was used for paired sample correlation analysis. The level of significance $p \le 0.05$ was assumed.

### Results

Table 1 presents demographic and clinical characteristics of the groups.

Biomicroscopy found no changes in the optical media or retina. The IOP values were within the normal range. Based on testing with the Mollon-Reffin test, [14] most subjects were normal trichromats, and one patient in Group 1 had a reduced blue color perception (D1P1T2).

The contrast sensitivity threshold at high spatial frequencies was significantly ($p < 0.05$) lower in the patient group as opposed to the control group.

Table 2 presents contrast sensitivity thresholds for both groups.

The contrast sensitivity threshold at high spatial frequencies was negatively correlated with disease duration (p=0.046, r=-0.585) (Fig. 2).

OCT-based macular parameters and the diameter of the foveola tended to increase compared with controls, but only differences in the macular volume ($p = 0.035$), superior inner retinal thickness ($p = 0.022$) and nasal inner retinal thickness ($p = 0.003$) for both eyes were significant.

All parameters excepting the diameter of the foveola and retinal foveal thickness were significantly increased in patients of Subgroup A (those with a disease duration longer than 5 years) compared to controls. However, there was no significant difference in any parameters in patients of Subgroup B (those with a disease duration shorter than 5 years) compared to controls (Tables 3 and 4).

It is of note, that, a patient with exacerbated hallucinosis and a practically continuous disease course (with no remission for 12 years) exhibited the greatest macular volume among patients of Group 1, with average retinal thickness and macular volume of 297.3 μm and 8.40 mm³, respectively, for the right eye, and 299.3 μm and 8.46 mm³, respectively, for the right eye. No correlation was found between the size of the foveola and the contrast sensitivity threshold for high (r=0.07), medium (r=0.153), and low spatial frequencies (r=0.168). The size of the foveola is associated with the axial length and may give indirect evidence of the density of foveal receptive fields (Fig. 3).

We found no significant differences in morphometric parameters of the optic disc or RNFL thickness between the two groups (Table 5).

### Discussion

Our finding of significantly increased contrast sensitivity threshold for high spatial frequencies in patients with schizophrenia confirms previously reported evidence of dysfunction of the parvocellular visual channels in the early disease stages [4].

Neuromediator theory of schizophrenia involves the idea of the possible existence of the dopaminergic system dysfunction and differences in the functional status of mesocortical and mesolimbical dopaminergic systems. This may be manifested ultrastructurally by the

development of atrophic or compensatory changes in the neuronal structures such as the retina [15]. Recent OCT studies in patients with schizophrenia have demonstrated contradictory results. Many of these studies reported reduced RNFL thickness [16], sometimes in combination with reduced macular volume and reduced retinal macular thickness [17-19], in patients with schizophrenia. In addition, the incidence of these changes increases with disease duration, which may be associated with prolonged psychotropic drug therapy and secondary atrophy of dopaminergic retinal cells. It has been reported that certain antipsychotics can cause degenerative retinopathies with features similar to those of primary retinitis pigmentosa. Some underlined the role of the drug effects on the activity of the retinal enzymatic systems preventing phototoxic effects. Others hypothesized that neuroleptic induced blockade of retinal D2/D4 receptors is among the initial events of these drug-induced degenerative retinopathies [20]. A study by Silverstein and colleagues [21] found no difference in RNFL or macula thickness between patients with schizophrenia and controls, but the former demonstrated enlarged optic disc parameters such as Cup Volume and C/D Area Ratio in both eyes. Of note is that the above study presented no values for optic disc area (Disc Area). It is known that the Cup Area, Rim Area and their ratio directly depend on the optic disc area (Disc Area). In macrodiscs with a normal Rim Area, C/D Area Ratio may be symmetrically increased [22]. A recent OCT study of patients with schizophrenia [17] found that, compared with controls, non-recent illness episode (NRIE) patients, but not recent illness episode (RIE) patients had significantly reduced RNFL overall measures, superior RNFL, nasal RNFL, macular volume, and macular inner ring thickness.

Therefore, our findings and those from other studies strongly suggest that patients with acute schizophrenia have an increased retinal macular thickness. Given that most patients in our schizophrenia group (10 of 12) had acute disease during the study, our findings may confirm the hypothesis that there is an association of an acute psychotic episode with neuroinflammation and subclinical retinal edema in the macula.

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**Table 1.** Clinical and demographic characteristics of the groups

| Characteristic | Group 1 | Group 2 |
|---|---|---|
| Numbers of subjects/ eyes | 12/24 | 12/24 |
| Age, years | 27.6 (18-37) | 28.3 (19-36) |
| Men/women | 8/4 | 6/6 |
| Best corrected visual acuity | 1.0 | 1.0 |
| Mean refractive error (D) | -1.25 ± 0.9 | -2.0 ± 2.1 |
| Mean axial length (mm) | 24.3 ± 0.7 | 24.4 ± 1.1 |
| Numbers of patients with disease duration of more than 5 years (subgroup A)/ less than 5 years (subgroup B) | 6/6 | – |
| Numbers of patients administered atypical antipsychotic drugs/ typical antipsychotic drugs | 10/2 | – |

**Table 2.** Contrast sensitivity threshold (CST) at high, moderate and low spatial frequencies (SF) for the schizophrenia group (Group 1) and the control group (Group 2)

| Subjects | CST at high SF (cycles per degree of visual angle) | CST at moderate SF (cycles per degree of visual angle) | CST at low SF (cycles per degree of visual angle) |
|---|---|---|---|
| Group 1 | 5.68 ± 1.89 | 17.83 ± 4.38 | 16.34 ± 3.96 |
| Group 2 | 7.18 ± 1.52 | 18.26 ± 4.73 | 18.68 ± 3.3 |

**Table 3.** Changes in the macula for the schizophrenia group (Group 1; subgroups A and B) and the control group (Group 2)

| Subjects | Group 1 | | Group 1 (mean values) | Group 2 |
|---|---|---|---|---|
| | Subgroup A (disease duration of > 5 years) | Subgroup B (disease duration of < 5 years) | | |
| Average Thickness, μm | 280.99 ± 10.27 | 273.41 ± 11.23 | 277.20 ± 11.21 | 272.24 ± 7.60 |
| Foveal Thickness, μm | 224.83 ± 30.08 | 208.17 ± 24.50 | 216.50 ± 28.15 | 211.96 ± 25.69 |
| Superior Thickness, μm | 318.50 ± 12.10 | 309.08 ± 14.72 | 313.79 ± 14.03 | 305.21 ± 7.40 |
| Nasal Thickness, μm | 318.33 ± 14.04 | 310.33 ± 14.96 | 314.33 ± 14.76 | 303.38 ± 9.79 |
| Temporal Thickness, μm | 301.58 ± 13.98 | 292.83 ± 14.28 | 297.21 ± 14.52 | 290.92 ± 7.23 |
| Inferoior Thickness, μm | 310.17 ± 14.14 | 300.58 ± 11.78 | 305.38 ± 13.63 | 298.96 ± 8.63 |
| Macular Volume, mm$^3$ | 7.98 ± 0.31 | 7.73 ± 0.32 | 7.86 ± 0.33 | 7.64 ± 0.19 |
| Fovea Length, μm | 423.42 ± 82.82 | 414.50 ± 48.74 | 418.96 ± 66.61 | 416.00 ± 73.18 |

**Table 4.** Significance of difference for changes in the macula for the schizophrenia group (Group 1; subgroups A and B) and the control group (Group 2)

| Parameters | Multiple comparison (ANOVA) | Pairwise comparison of groups 1 and 2 (Mann-Whitney test) | Pairwise comparison of group 2 and Subgroup A (Mann-Whitney test) | Pairwise comparison of group 2 and Subgroup B (Mann-Whitney test) |
|---|---|---|---|---|
| Average Thickness, µm | 0.032* | 0.119 | 0.03* | 0.712 |
| Foveal Thickness, µm | 0.268 | 0.542 | 0.195 | 0.762 |
| Superior Thickness, µm | 0.005* | 0.022* | 0.002* | 0.568 |
| Nasal Thickness, µm | 0.005* | 0.003* | 0.002* | 0.072 |
| Temporal Thickness, µm | 0.031* | 0.056 | 0.020* | 0.430 |
| Inferior Thickness, µm | 0.019* | 0.055 | 0.015* | 0.480 |
| Macular Volume, mm$^3$ | 0.002* | 0.035* | 0.003* | 0.603 |
| Fovea Length, µm | 0.943 | 0.765 | 0.908 | 0.712 |

Note: *, significant difference

**Table 5.** Optic disc measurements for the schizophrenia group (Group 1) and the control group (Group 2)

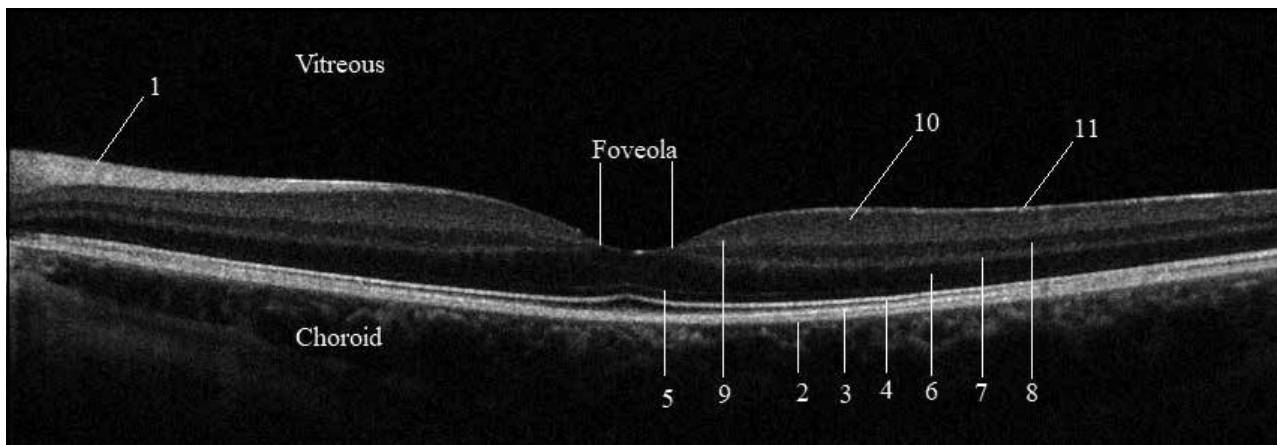| Subjects | Group 1 | Group 2 | Two-tailed significance (p) |
|---|---|---|---|
| RNFL Total, µm | 96.63 ± 6.72 | 93.88 ± 7.82 | 0.198 |
| Disc Area, mm$^3$ | 2.27 ± 0.27 | 2.23 ± 0.21 | 0.488 |
| Rim Area, mm$^3$ | 1.54 ± 0.59 | 1.45 ± 0.56 | 0.605 |
| C/D Area Ratio | 0.23 ± 0.14 | 0.27 ± 0.15 | 0.448 |

**Fig. 1.** Representative OCT image of the retina of a patient with paranoid schizophrenia. Note: 1, retinal nerve fiber layer; 2, RPE/Bruch's membrane complex; 3, interdigitation zone representing the interdigitation of the apical processes of the RPE with cone outer segments; 4, ellipsoid zone of photoreceptors; 5, external limiting membrane; 6, outer nuclear layer; 7, outer plexiform layer; 8, inner nuclear layer; 9, inner plexiform layer; 10, ganglion cell layer; 11, internal limiting membrane
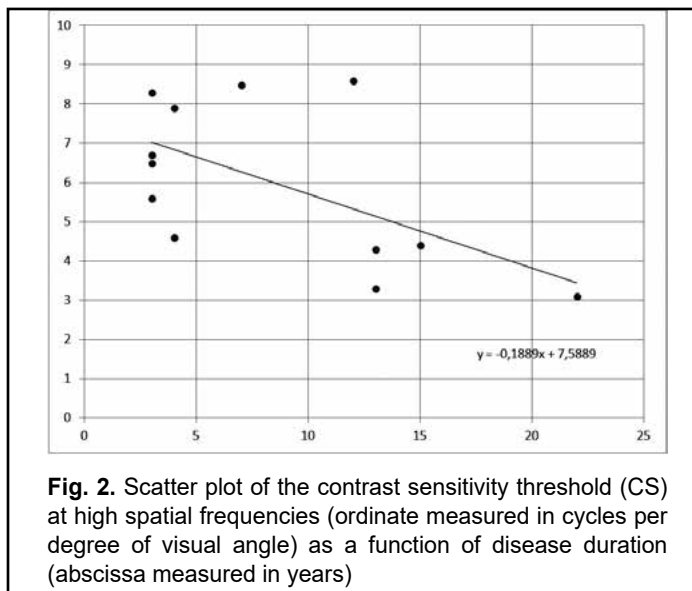


**Fig. 2.** Scatter plot of the contrast sensitivity threshold (CS) at high spatial frequencies (ordinate measured in cycles per degree of visual angle) as a function of disease duration (abscissa measured in years)
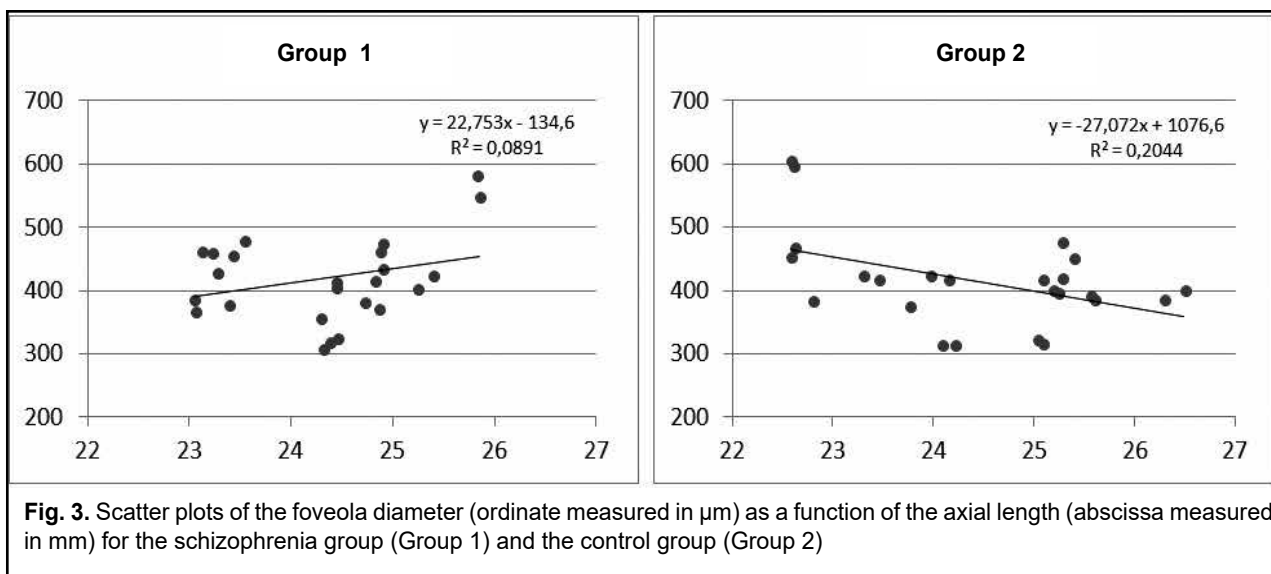


**Fig. 3.** Scatter plots of the foveola diameter (ordinate measured in µm) as a function of the axial length (abscissa measured in mm) for the schizophrenia group (Group 1) and the control group (Group 2)