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ORIGINAL PAPER

Clinical and biological correlates of optical coherence tomography findings in schizophrenia

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Abstract

There is a growing body of evidence indicating retinal layer thinning in schizophrenia. However, neuropathological processes underlying these retinal structural changes and its clinical correlates are yet to be known. Here, we aim to investigate the clinical and biological correlates of OCT findings in schizophrenia. 50 schizophrenia patients and 40 healthy controls were recruited. Retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), and macular and choroidal thicknesses were recorded. A comprehensive battery of neuropsychological tests was applied. Fasting glucose, triglycerides and HDL-cholesterol levels, TNF-α, IL-1β and IL-6 levels were measured. Right IPL was significantly thinner in patients than the controls after controlling for various confounders ($F=5.42$, $p=.02$). Higher IL-6, IL-1β, and TNF-α levels were associated with decreased left macular thickness ($r=-0.26$, $p=.027$, $r=-0.30$, $p=0.012$, and $r=-0.24$, $p=.046$, respectively) and higher IL-6 was associated with thinning of right IPL ($r=-0.27$, $p=0.023$) and left choroid ($r=-0.23$, $p=.044$) in the overall sample. Thinning of right IPL and left macula were also associated with worse executive functioning ($r=0.37$, $p=0.004$ and $r=0.33$, $p=0.009$) and attention ($r=0.31$, $p=0.018$ and $r=0.30$, $p=0.025$). In patients with schizophrenia, IPL thinning was associated with increased BMI ($r=-0.44$, $p=0.009$) and decreased HDL levels ($r=0.43$, $p=0.021$). Decreased TNF-α level was related to IPL thinning, especially in the left eye ($r=0.40$, $p=0.022$). These findings support the hypothesis that OCT might provide the opportunity to establish an accessible and non-invasive probe of brain pathology in schizophrenia and related disorders. However, future studies investigating retinal structural changes as a biological marker for schizophrenia should also consider the metabolic state of the subjects.

Keywords Schizophrenia · OCT · Retinal thickness · Cytokine · Cognition

Introduction

Schizophrenia (SCZ) is a chronic debilitating mental disorder which is characterized by cognitive dysfunction including deficits in memory/learning, attention, and executive function [1]. Neuroimaging studies have revealed that there are some structural changes in patients, such as ventricular enlargement and grey matter volume reduction, which suggest parallels between neurodegenerative disorders and schizophrenia [2–4]. Despite the controversial results, a large number of studies have indicated that these changes are correlated with the level of cognitive impairment [5]. Genetic and environmental factors are blamed on etiology, yet, to date, there has not been a clearly defined neuropathological explanation of the disorder. Immune system has gained increasing attention as being integrally involved in etiopathogenesis [6–8]. Genome-wide association studies

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suggest that the polymorphisms vulnerable to schizophrenia are located on chromosome 6p22 which also contains many immune-related genes including those involved in antigen presentation and inflammatory mediators [9]. A growing body of evidence in both chronic and first-episode schizophrenia report increased expression of proinflammatory substances such as cytokines in the blood and cerebrospinal fluid of patients that results in schizophrenia being considered as a chronic low-grade inflammatory disease [10]. Several studies have also shown that abnormal immune response is associated with central structural changes such as decreased hippocampal volume and ventricular enlargement [11–14] and cognitive deterioration in patients with schizophrenia [13, 15].

The retina originates from the forebrain neuroectoderm and displays many similarities with the central nervous system (CNS) in terms of functionality, anatomy, neurotransmitters, and immunology [16]. Because of this, it has been viewed as an extension of the brain by many investigators [17–19]. In vivo visualization of the retina can be achieved by Optical Coherence Tomography (OCT) which provides a high-resolution cross-sectional image of the retinal layers, such as the ganglion cell layer (GCL), inner plexiform layer (IPL), retinal nerve fiber layer (RNFL), and choroid. The choroid is the vascular layer of the eye, which provides oxygen and nourishment to the outer retina. The GCL consists of bodies of ganglion cells, and the IPL consists of dendrites of ganglion cells and postsynaptic connections. The RNFL is comprised of unmyelinated axons of retinal ganglion cells that converge to form the optic nerve which projects to the lateral geniculate nucleus of the thalamus and provides sensory inputs to the visual cortex. It is hypothesized that neuronal damage/synaptic dysfunction occurring at any stage of this pathway can lead to retrograde transsynaptic axonal degeneration (RTSD) resulting in decreased RNFL, GCL, or IPL thickness [20]. The thalamus has many connections with the cerebral cortex, striatum, and cerebellum acting a hub-like exchange of information and modulates several cognitive domains. It is one of the brain regions that is most affected in schizophrenia in the means of neuronal density, volume, connectivity, and functionality [21]. Therefore, neuronal damage caused by abnormal inflammatory response may result in retinal thinning through RTSD mechanism. In this regard, OCT might be a promising, novel technique to provide an opportunity to indirectly assess neurovasculature, neuroinflammation, and neurodegeneration in the CNS [22]. Based on this point, it has been used in many neurological disorders, such as Parkinson's disease, Alzheimer's disease (AD), and multiple sclerosis (MS), in recent years [23–26]. Data come from these studies indicate that the thinning of retinal layers correlates with CNS atrophy and other disease characteristics. For example, reduced RNFL thickness is correlated with MRI measures of brain atrophy in MS [27]. RNFL thinning is also related to cognitive decline in AD [26, 28] and brain volume loss in ageing [29, 30], and is predictive of developing dementia later on [31].

As evidence suggests a degenerative component for schizophrenia, OCT has been used to assess retinal layer changes in schizophrenia patients. Several studies indicated a significant reduction in RNFL or macular thicknesses [32–36], as well as thinning of GCL and IPL in schizophrenia [37]. More recently, alterations in outer retinal layers have also been investigated. Samani et al. (2017) revealed a thinning of the outer nuclear layer and inner segment layer, as well as reduced total retinal and photoreceptor thicknesses [38]. Recent meta-analyses demonstrated the thinning of RNFL and GC-IPL layers in patients [20, 21, 39] with the effect size for RNFL being similar to the strongest single structural alterations reported in schizophrenia. However, not all studies have demonstrated these effects [17, 40] and studies suggest that these changes might be affected by disease-related variables, such as phase and duration of the illness and comorbid medical conditions. Lee et al. (2013) reported a decreased RNFL and macular thickness in only patients with a longer duration of illness, not in those with less than 2 years since illness onset [33]. In another study, Ascaso et al. (2015) found a significantly decreased RNFL thickness and macular volume in patients with schizophrenia, but this difference was only evident in patients who had not experienced a recent illness episode [34]. In Silverstein et al.'s study (2018), patients and controls did not differ on RNFL, GC-IPL or macular thicknesses and the thinning of these layers was found associated with the presence of hypertension or diabetes, rather than illness itself [40].

Despite previous studies showing a correlation between retinal thinning and cognitive impairment in neurodegenerative diseases, the relationship between cognitive impairment and retinal layer changes in schizophrenia remains unclear and there are only a few recent studies in the literature on this point. In the first preliminary study with a heterogeneous small sample, Bannai et al. (2021) investigated the association of retinal abnormalities with cortical measures and cognitive functions and found that thinning of the outer nuclear layer was associated with worse cognitive functions and smaller total brain and white matter volume in the overall sample. However, in the patient group, none of the retinal layers was associated with cognitive scores, but thinning of RNFL was associated with smaller total brain and grey matter volume and thinning of the inner nuclear layer was associated with smaller total grey matter volume [41]. In the second study by Liu et al. (2020), the reduction of RNFL was found to correlate with the decreased immediate memory and visuospatial function subscale scores of RBANS (Repeatable Battery for the Assessment of Neuropsychological Status), while the other domains, such as language, attention, and delayed memory, were not found correlated [42]. More recently, the same group indicated that thinning of RNFL was associated with worse performance on Stroop-color word reading time but not with word color naming time in schizophrenia [36].

Taken together, despite early OCT studies suggesting that retinal thinning might be a marker of vascular, inflammatory, or degenerative processes which could occur in the brain of schizophrenia patients, findings in this developing field of research are currently contradictory and seem to be affected by several disease-related factors. Therefore, before proposing OCT findings as a biomarker for schizophrenia, further studies are needed to determine the biological and clinical correlates of retinal structural alterations and to explore potential neuropathological processes that underlie these findings.

In this study, we aimed to explore retinal structural alterations in patients with schizophrenia and to determine the relationship between retinal structures and clinical symptoms including cognitive functions, such as executive function, attention, and memory, and the inflammatory and cardiometabolic status of participants. Based on previous findings in the literature mentioned in detail above, we hypothesized that patients with schizophrenia would show reduced retinal thicknesses and predicted that retinal thinning would be associated with impaired performance on domain-specific cognitive tasks and a higher inflammatory stage. We also hypothesized that worse cardiometabolic status would be associated with more prominent changes in OCT.

Methods

Sample

This study was performed on patients who applied to the outpatient services of Bezmialem University, Department of Psychiatry or who have been followed by the Fatih Community Mental Health Centre. Fifty chronic schizophrenia patients and 40 age- and gender-matched healthy controls were recruited into the study. Of these, 7 patients were excluded (3 withdrew their consent, 1 could not cooperate in the ophthalmologic examination, and 3 had ocular pathology) and 43 patients and 40 controls were included in the final analyses. The sample was based on a priori power analysis, showing that 35 participants would be required in each group for 90% power to detect a 5% difference in RNFL thickness at the 0.05 level of significance [34]. All participants were Caucasian. Primary diagnosis of schizophrenia and comorbid psychiatric disorders were ascertained by the Structured Clinical Interview for DSM-IV-TR (SCID). Control subjects were excluded if they had any psychiatric disorder, a previous history of psychotic or mood disorders or a family history of bipolar or schizophrenia spectrum disorder. All subjects were between 22 and 64 years old. Exclusion criteria for both groups were as follows: (a) glaucoma, uveitis, cataract, vitreous opacities, macular degeneration, or diabetic retinopathy, (b) any previous ocular surgery or trauma, (c) Any neurological or systemic disease known to affect the visual system, (d) previous or concurrent autoimmune diseases, (e) spherical equivalent of refractive error of < -6 D or $> +6$ D, f) mental retardation, (g) illiteracy, (h) acute psychosis, (i) comorbid axis 1 psychiatric disorder, and (j) substance or alcohol misuse.

Measurements

A sociodemographic form prepared by the researcher was used to collect information about age, gender, education, duration of the illness, and comorbid medical diseases. Schizophrenic symptomatology was assessed using the Positive and Negative Syndrome Scale (PANSS). Ongoing psychotropic treatment, BMI, and tobacco smoking were also recorded. Chlorpromazine equivalent doses for antipsychotic medications were generated by calculating the percentage of BNF maximum daily doses (https://www.bnf.org/).

Neuropsychological measures

Wisconsin card sorting test

The Wisconsin Card Sorting Test (WCST) was used to examine executive functions such as category shifting, persistence, mental control, strategic planning, and organization [43]. The computerized version of WCST was used, and performances were scored by the computer. Dependent variables were the number of correct answers, the number of perseverative errors and the number of categories completed.

Stroop test

Stroop Test measures selective attention and executive functioning as well as processing speed and cognitive flexibility [44]. The TBAG form was used in this study. The time difference between color and word reading tasks ("Part 2" and "Part 5") and the number of mistakes in the color task ("Part 5") provided the performance measures.

Verbal memory processes test

The Verbal Memory Processes Test (VMPT) is an analogue of the Rey Auditory Verbal Learning test in the Turkish language [45]. In the test, a word list of 15 words is read to the subject ten times. Immediate memory score (the number of words recalled in the first trial), total learning score (the total number of words recalled in all trials), and delayed free recall score (the number of words recalled following a 40 min delay) were the performance measures.

The trail making test

The Trail Making Test (TMT) assesses attention, test shifting, cognitive flexibility, and processing speed. It consists of two parts, A and B. The participants are evaluated on the time taken to complete each part of the test [46]. The time difference between Part B and A (B-A) was considered as the final score in this study.

OCT measures

Prior to OCT assessment, all participants underwent a comprehensive ophthalmic examination including slit-lamp biomicroscopy, intraocular pressure measurement, corrected visual acuity measurement and indirect ophthalmoscopy. Retinal imaging was performed using the Spectralis OCT device without pupil dilation (version 6.9, Heidelberg Engineering, Heidelberg, Germany) for both eyes of the subjects. For peripapillary RNFL measurement, circumpapillary scans of 3.4 mm diameter centered on the disc were obtained using the Heidelberg Eye Explorer software (version 1.9.10.0) and measurements were performed at 7 regions: the central circle with diameter 1-mm (global region) and superotemporal, temporal, inferotemporal, inferonasal, nasal, and superonasal peripapillary quadrants. All images were assessed by an experienced investigator (AE) who was blinded to the diagnosis of participants to confirm that the scan was centered and the segmentation was properly delineated. The quality of measurements was assessed by Q score and scans with a Q score greater than or equal to 30 were included in the study.

The horizontal scan crossing through the fovea was taken as a screening line to evaluate IPL and GCL. IPL and GCL thicknesses were measured from nasal and temporal poles at a distance of 1000 μm to the fovea. To evaluate the choroidal thickness, OCT scans were acquired through the fovea with the horizontal 30-line-scan enhanced depth imaging mode of the device. The distance between the outer layer of the retinal pigment epithelium and the choroid–scleral junction was evaluated as choroidal thickness. Measurements were performed manually at the central fovea and at the 1000 μm nasal and temporal sides to the fovea by two investigators who were blinded to the participants' diagnoses (interclass correlation was 0.92 (0.86–0.95) for GCL and 0.90 (0.84–0.94) for IPL). Mean choroidal thickness was calculated by averaging the values of three regions. As several studies revealed that choroidal thickness is subjected to diurnal variations, OCT measurements were performed at the same time of the day (9.30–11.30 am).

Biochemical measures

Venous blood samples were taken from subjects after a minimum of 8 h fasting, between 8.30 AM and 10.30 AM on the same day of OCT scans. Then, samples were separated by centrifugation and stored at − 80 ℃ until subsequent analyses. Triglycerides, HDL and glucose analyses were determined by standard clinical laboratory methods using certified assays at Bezmialem Vakif University Hospital's clinical laboratory. TNF-α, IL-1β, and IL-6 levels were measured using a commercial ELISA kit (Eastbiopharm—Human TNF Alpha ELISA Kit, Cat.No: CK-E10110, Eastbiopharm—Human IL1 Beta ELISA Kit, Cat.No:CK- E10083, Eastbiopharm—Human IL-6 ELISA Kit, Cat.No:CK-E10140) following the indications of the manufacturer. Absorbance at 450 nm was measured with an ELISA plate reader (Thermo Scientific™ Varioskan™ Flash Multimode Reader) and the results were expressed in ng/L and pg/L.

Statistical analyses

All statistical analyses were performed using SPSS version 25 (SPSS Inc., Chicago, IL) for Macintosh. Group difference in sociodemographic and clinical characteristics was analyzed using the Chi-square test for categorical variables and Student's *t* test for normally distributed and Mann–Whitney *U* test for non-normally distributed continuous variables. Differences between study groups on retinal thicknesses and inflammatory cytokines were first analyzed using the Student's *t* test. For the comparisons that show a significant or trend-level difference between groups, an ANCOVA was used to adjust the analyses for age, gender, smoking status, and metabolic parameters. Between eye differences were compared by paired sample *t* test.

To use in our further analyses and to avoid false-positive results of multiple testing, we generated Z-scores for each neurocognitive test subscore and then calculated compound scores for executive functioning, attention, and memory/learning. As lower scores indicate better performance, scores of Stroop-color error, Stroop-time difference, TRM-time difference, and WCST-perseverative error scores were multiplied by − 1. Then, we calculated the compound score for attention by averaging these Stroop-color error, Stroop-time difference, and TRM-time difference Z-scores. Z-scores of WCST—the number of correct answers, categories completed, and perseverative errors were averaged to calculate the compound executive functioning score. The compound score for memory/learning was calculated by averaging the Z-scores of VMPT- immediate memory, total learning score, and delayed free recall.

Association between OCT measures and clinical and biological variables were assessed using Pearson or Spearmen correlation test depending on the distribution of variables.

Results

Sociodemographic and clinical characteristics of the study groups

Sociodemographic and clinical characteristics of the study sample are presented in Table 1. The groups were well matched in age ($t = 1.44$, $p = 0.15$), gender ($\chi^2 = 0.51$, $p = 0.62$), and smoking status ($\chi^2 = 0.26$, $p = 0.77$). In terms of the metabolic parameters, the groups did not differ in BMI, triglycerides, or HDL-cholesterol levels ($t = 1.02$, $p = 0.31$; Z = −0.24, $p = 0.81$ and Z = −0.86, $p = 0.39$, respectively). However, fasting glucose level was significantly higher in the patient group ($t = 2.93$, $p = 0.005$).

Cognitive test scores of participants are also illustrated in Table 1. All items were significantly different between the study groups (Table 1).

Proinflammatory cytokine levels by study groups

Proinflammatory cytokine levels by study groups are illustrated in Fig. 1. There was a significant group difference in all three cytokine levels and patients had higher mean values for TNF-α, IL-1β and IL-6 compared to HCs (Means and SDs for each group were as follows: TNF-α 118.28 ± 10.92 for SCH and 60.29 ± 9.08 for HCs; IL-1β 363.27 ± 37.27 for SCH and 95.78 ± 16.08 for HCs; IL-6 67.02 ± 14.89 for SCH and 19.72 ± 6.18 for HCs). Between-group differences in cytokine levels remained significant after controlling for age, gender, BMI, glucose, HDL, triglycerides levels, and smoking status ($\beta = -0.97$, $t = -32.78$, $p < 0.001$; $\beta = -0.89$, $t = -15.63$, $p < 0.001$; $\beta = -0.98$, $t = -22.20$, $p < 0.001$, for IL-1β, IL-6, and TNF-α, respectively).

Differences between groups in retinal thicknesses.

As shown in Table 2, right IPL and left macula thicknesses were significantly decreased in patients compared to

Table 1 Sociodemographic and clinical characteristics of participants

	SCZ (n = 50)		HC (*n* = 40)		p	Test statistics
	N	%	N	%		
Gender (female%)	20	40	19	43.3	0.62	χ2 = 0.51
Age (years)	42.38 ± 10.95		38.90 ± 11.91		0.15	t = 1.44
Education (years)	7.76 ± 3.98		11.10 ± 5.39		0.002*	t = -3.31
Smoking status (smoker%)	26	45.8	19	48.7	0.77	χ2 = 0.26
BMI (kg/m^2)	28.22 ± 5.97		27.00 ± 5.03		0.31	t = 1.02
Glucose (mg/dl)	101.57 ± 20.75		91.42 ± 7.92		0.005*	t = 2.93
HDL (mg/dl)	46.23 ± 12.06 (35.92)		47.42 ± 9.88 (40.25)		0.39	Z = -0.86
Triglycerides (mg/dl)	145.74 ± 117.96 (37.41)		143.11 ± 96.62 (38.64)		0.81	Z = -0.24
CRP (mg/dl)	0.90 ± 1.71 (38.7)		0.38 ± 0.56 (37.3)		0.77	Z = -0.29
Cognitive tests						
Attention						
Stroop-color error	2.96 ± 5.97 (49.8)		0.51 ± 0.94 (35.0)		0.002*	Z = -3.01
Stroop-interference (sec)	26.07 ± 16.17 (51.20)		15.85 ± 9.55 (31.97)		< 0.001*	Z = -3.60
TMT-Part B-A (sec)	118.56 ± 74.02 (44.35)		69.97 ± 53.25 (29.44)		0.003*	Z = -3.00
Memory						
VMPT-immediate memory	4.02 ± 1.64 (33.3)		5.67 ± 1.84 (53.1)		< 0.001*	Z = -3.82
VMPT-total learning score	72.44 ± 21.53		108.03 ± 22.47		< 0.001*	t = -7.36
VMPT-delayed free recall	6.33 ± 2.95 (27.6)		10.89 ± 3.06 (56.2)		< 0.001*	Z = -5.48
Executive function						
WCST-Correct answers	60.00 ± 17.44		73.49 ± 24.04		0.007*	t = -2.80
WCST-Perseverative error	42.35 ± 20.74		30.00 ± 19.66		0.01*	t = 2.64
WCST-Categories	1.74 ± 1.16 (29.7)		4.22 ± 3.03 (47.8)		< 0.001*	Z = -3.62
Disease characteristics						
Duration of illness (years)	18.44 ± 9.84					
PANSS-Total score	66.49 ± 14.50					
CPZe (mgs)	737.70 ± 473.03					

SCH Schizophrenia patients, *HC* Healthy controls, *BMI* Body mass index, *HDL* High-density lipoprotein, *TMT* Trail making test, *VMPT* Verbal memory processes test, *WCST* Wisconsin card sorting test, *PANSS* Positive and negative syndrome scale, *CPZe* Chlorpromazine equivalent dose

*$p < 0.05$

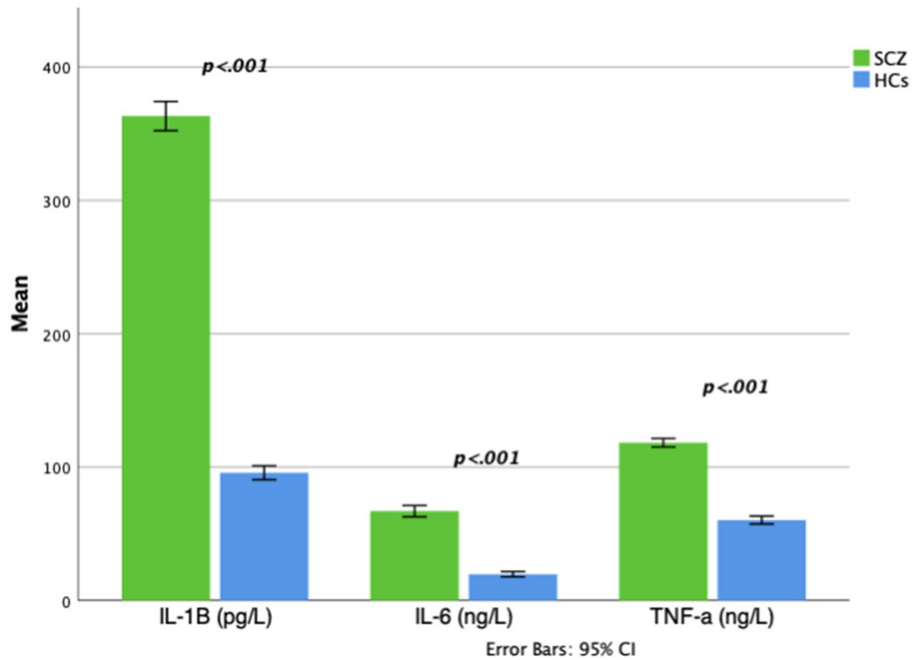

Fig. 1 Comparison of proinflammatory cytokine levels by study groups. All comparisons between schizophrenia (SCZ) and healthy control (HCs) subjects were statistically significant at $p<0.001$

controls ($t=-2.49$, $p=0.02$ and $t=-2.31$, $p=0.02$, respectively). After adjusting for age, gender, BMI, glucose, HDL, and triglycerides levels, the difference between study groups in right IPL thickness remained significant, particularly in the temporal segment ($F=5.42$, $p=0.02$ for mean IPL and $F=6.80$, $p=0.01$ for temporal IPL).

Our post hoc analyses revealed that global ($t=-2.35$, $p=0.025$), temporal ($t=3.87$, $p<0.001$), superonasal ($t=-4.43$, $p<0.001$) and nasal ($t=4.47$, $p<0.001$) RNFL, and subfoveal choroidal ($t=2.31$, $p=0.027$) thicknesses were significantly different between left and right eyes of healthy controls. However, only temporal ($t=2.42$, $p=0.021$) and superonasal ($t=-2.71$, $p=0.01$) RNFL thicknesses showed between-eye differences in patients.

Inflammatory and metabolic correlates of OCT measures

In the overall sample, there was a negative correlation between IL-6 level and right IPL and left choroidal thicknesses. Decreased left macular thickness was also associated with the increased levels of IL-6, IL-1β, and TNF-α (Supplementary Table 1). In the patient group, IL-6 was negatively correlated with left choroidal thickness, whereas TNF-α was positively correlated with left IPL thickness. There was also a non-significant trend-level positive correlation between right IPL thickness and TNF-α, and a negative correlation between right RNFL and IL-1β (Table-3). TNF-α level was also positively correlated with right choroidal thickness ($r=0.35$, $p=0.04$) and right RNFL ($r=0.32$, $p=0.06$) in healthy controls and a trend-level negative correlation was observed between IL-6 and left macula ($r=-0.32$, $p=0.06$).

With regards to metabolic parameters, higher triglycerides' level was associated with lower right GCL thickness, and higher BMI and glucose levels were associated with lower left GCL thickness in the overall sample (Supplementary Table 1). In the patient group, right GCL thickness was negatively correlated with glucose levels and right RNFL and right IPL thicknesses were positively correlated with HDL levels. BMI was negatively correlated with right IPL and macula thicknesses but surprisingly positively correlated with right choroidal thickness (Table 3). In healthy controls, left choroidal thickness was negatively correlated with triglycerides levels ($\rho=-0.55$, $p<0.001$).

Clinical correlates of OCT measures

In the overall sample, a lower executive functioning compound score was associated with decreased right and left IPL and right and left macular thicknesses. There was also a significant correlation between attention compound score and right IPL and left macular thicknesses (Supplementary Table 1).

In the patient group, there was no statistically significant correlation between OCT measures and cognitive compound scores; however, a trend-level positive correlation was observed between left IPL thickness and executive functioning score (Table 3). Post hoc analyses revealed that the only subscale score that showed a statistically significant correlation with OCT measures was the immediate memory score. Higher VMPT-immediate memory score was associated

Table 2 Descriptive and inferential analyses of retinal thicknesses (μm) by study groups

	Descriptive analyses		Inferential analyses				
	Mean ± SD		Unadjusted			Adjusted[1]	
	Patients	Controls	*t*	*p*	*η*2	*F*	*p*
Right eye							
RNFL-global	100.22 ± 10.50	100.36 ± 8.91	− 0.06	0.95			
Superotemporal	138.24 ± 21.66	136.81 ± 17.75	0.31	0.76			
Temporal	73.65 ± 12.18	71.32 ± 12.26	0.82	0.42			
Inferotemporal	141.24 ± 25.84	142.42 ± 21.72	− 0.21	0.83			
Inferonasal	114.00 ± 24.31	121.44 ± 21.10	− 1.40	0.17			
Nasal	76.92 ± 19.99	78.39 ± 12.25	− 0.38	0.71			
Superonasal	106.05 ± 16.23	107.68 ± 16.22	− 0.43	0.67			
GCL (mean)	48.38 ± 5.83	48.53 ± 7.40	− 0.09	0.93			
Temporal	46.77 ± 6.48	44.24 ± 8.29	1.48	0.15			
Nasal	49.63 ± 8.55	52.81 ± 7.49	− 1.73	0.09†	0.02	0.85	0.36
IPL (mean)	40.50 ± 3.54	42.70 ± 4.06	− 2.49	0.02*	0.10	5.42	0.02*
Temporal	39.19 ± 4.10	42.05 ± 5.24	− 2.62	0.01*	0.12	6.80	0.01*
Nasal	42.33 ± 5.12	43.35 ± 4.88	− 0.90	0.37			
Choroid (mean)	279.18 ± 76.73	297.00 ± 54.03	− 1.15	0.25			
Temporal	264.49 ± 68.10	286.41 ± 61.53	− 1.47	0.15			
Subfoveal	296.30 ± 86.92	304.24 ± 72.95	− 0.43	0.67			
Nasal	271.58 ± 87.15	274.19 ± 77.82	− 0.14	0.89			
Macula	214.30 ± 15.11	218.84 ± 15.37	− 1.31	0.20			
Left eye							
RNFL-global	99.82 ± 9.88	98.39 ± 8.99	0.66	0.52			
Superotemporal	134.85 ± 18.31	133.89 ± 15.53	0.24	0.81			
Temporal	71.39 ± 12.49	66.97 ± 11.42	1.60	0.11			
Inferotemporal	145.28 ± 22.00	141.92 ± 22.02	0.67	0.51			
Inferonasal	112.64 ± 22.28	118.05 ± 19.29	− 1.13	0.26			
Nasal	73.03 ± 12.50	71.11 ± 12.85	0.66	0.51			
Superonasal	116.77 ± 26.63	120.41 ± 20.43	− 0.67	0.51			
GCL (mean)	48.41 ± 6.04	49.26 ± 7.40	− 0.52	0.60			
Temporal	46.43 ± 6.36	45.63 ± 7.65	0.48	0.64			
Nasal	50.40 ± 7.37	52.89 ± 8.06	− 1.35	0.18			
IPL (mean)	41.23 ± 5.44	42.40 ± 4.62	− 0.96	0.34			
Temporal	39.89 ± 6.35	41.20 ± 4.84	− 0.97	0.33			
Nasal	42.57 ± 5.61	43.57 ± 5.65	− 0.74	0.46			
Choroid (mean)	284.31 ± 92.40	313.10 ± 66.28	− 1.57	0.12			
Temporal	278.13 ± 94.17	301.13 ± 66.53	− 1.24	0.22			
Subfoveal	297.18 ± 98.43	334.79 ± 75.27	− 1.88	0.06†	0.03	1.49	0.23
Nasal	277.62 ± 94.92	303.37 ± 69.40	− 1.36	0.18			
Macula	210.21 ± 24.31	221.14 ± 15.21	− 2.31	0.02*	0.06	3.12	0.08†

RNFL retinal nerve fiber layer, *GCL* ganglion cell layer, *IPL* inner plexiform layer

*$p < 0.05$

†$p < 0.1$

[1]adjusted for age, gender, BMI, glucose, HDL and triglycerides levels

Table 3 Clinical and biological correlates of OCT measures in patients

	Right RNFL	Right GCL	Right IPL	Right macula	Right choroid	Left RNFL	Left GCL	Left IPL	Left macula	Left choroid
Biochemical measures										
IL-1β	− 0.31†	− 0.01	0.13	− 0.03	0.18	− 0.15	0.16	0.23	− 0.03	0.24
IL-6	− 0.03	− 0.11	− 0.09	0.07	− 0.21	− 0.07	− 0.17	− 0.03	0.08	− 0.35*
TNF-α	0.20	− 0.10	0.29†	0.18	0.03	0.23	0.11	0.40*	0.02	− 0.04
CRP	0.12	0.28	0.09	− 0.14	0.11	0.09	0.18	− 0.01	0.19	0.06
Glucose	0.14	− 0.34*	− 0.06	− 0.16	0.08	0.19	− 0.34†	− 0.17	− 0.22	− 0.01
HDL	0.44*	− 0.03	0.43*	0.13	0.06	0.19	0.03	− 0.02	0.08	− 0.02
Triglycerides	− 0.35†	− 0.32†	0.03	− 0.17	0.20	− 0.02	− 0.29	− 0.08	− 0.15	0.14
Clinical parameters										
BMI	0.14	− 0.13	− 0.44**	− 0.37*	0.36*	0.28	− 0.31†	− 0.34†	− 0.20	0.26
CPZe	− 0.21	− 0.32*	− 0.11	− 0.12	− 0.31*	− 0.33*	− 0.08	− 0.21	− 0.07	− 0.29†
PANSS-total	0.05	− 0.09	0.26	0.22	− 0.08	0.10	0.07	0.15	0.17	− 0.004
Disease duration	0.10	0.35*	0.47**	0.27†	− 0.13	0.05	0.24	0.35*	0.18	− 0.21
Cognitive tests										
Executive functioning[1]	− 0.25	− 0.04	0.22	0.10	0.24	− 0.22	0.12	0.36†	0.12	0.23
Attention[2]	0.13	− 0.13	0.06	− 0.11	0.13	0.11	− 0.06	0.01	0.07	0.18
Memory/learning[3]	0.20	− 0.15	− 0.22	− 0.06	0.13	0.24	− 0.03	0.19	0.11	0.06

TNF-α Tumor necrosis factor-alpha, *IL-1β* Interleukin 1β, *IL-6* Interleukin-6, *HDL* High-density lipoprotein, *BMI* Body mass index, *PANSS* Positive and Negative Syndrome Scale, *CPZe* Chlorpromazine equivalent

* $p < 0.05$

** $p < 0.01$

† $p < 0.1$

[1] Calculated by averaging the Z-scores of WCST-categories WCST-perseverative errors and WCST-correct answers

[2] Calculated by averaging the Z-scores of Stroop-color error, Stroop-interference, and TRMT-time difference

[3] Calculated by averaging the Z-scores of VMPT-immediate memory, VMPT-total learning score, and VMPT- delayed free recall

with thicker RNFL and choroidal measures for both eyes ($r=0.38$, $p=0.04$; $r=0.50$, $p=0.002$; $r=0.45$, $p=0.007$; $\rho=0.36$, $p=0.037$ for right RNFL, right choroid, left RNFL, and left choroid, respectively).

In the control group, both right and left IPL thicknesses were positively associated with compound executive functioning score ($\rho=0.42$, $p=0.017$ and $r=0.40$, $p=0.03$), and right GCL, right macula and left GCL were positively associated with attention score ($r=0.39$, $p=0.028$; $r=0.39$, $p=0.028$ and $r=0.41$, $p=0.021$, respectively) However, a negative association was observed between left RNFL and memory score ($r=-0.39$, $p=0.02$).

In terms of disease-related clinical parameters, there was no significant correlation between any of OCT measures and symptom severity in patients with schizophrenia. However, higher CPZe doses were associated with lower right GCL, right choroidal and left RNFL thicknesses. Interestingly, longer disease duration was associated with thicker right and left IPL and right GCL thicknesses (Table 3).

Correlation between inflammatory parameters and cognitive functions

In the overall sample, higher IL-1β, IL-6, and TNF-α levels were significantly correlated with worse performance in all cognitive domains, including memory, attention, and executive functioning. However, CRP level was not related to any of cognitive scores (Supplementary Table 2).

In patients with schizophrenia, higher CRP level was associated with worse executive functioning, but there was no significant correlation between cytokine levels and any of cognitive domains (Table 4).

In healthy controls, higher attention compound score was associated with increased level of IL-1β ($\rho=0.35$ and $p=0.042$), and there was a trend-level positive correlation between IL-6 and memory score ($r=0.31$ and $p=0.065$).

Table 4 Association of inflammatory markers and cognitive functions in patients with schizophrenia

	IL-1β	IL-6	TNF-α	CRP
Executive functioning[1]	0.25	− 0.16	− 0.11	− 0.40*
Attention[2]	0.13	0.004	0.09	− 0.25
Memory/Learning[3]	0.20	− 0.04	0.24	− 0.09

TNF-α Tumor necrosis factor-alpha, *IL-1β* Interleukin-1β, *IL-6* Interleukin-6, *CRP* C-reactive protein

*$p<0.05$

†$p<0.1$

[1]Calculated by averaging the Z-scores of WCST-categories WCST-perseverative errors, and WCST-correct answers

[2]Calculated by averaging the Z-scores of Stroop-color error, Stroop-interference, and TRMT-time difference

[3]Calculated by averaging the Z-scores of VMPT-immediate memory, VMPT-total learning score, and VMPT- delayed free recall

Discussion

In this study, we investigated metabolic, inflammatory, and domain-specific cognitive correlates of OCT findings in schizophrenia. First, our results revealed a significant decrease in right IPL and a trend-level decrease in left macular thicknesses in patients with schizophrenia after controlling for various confounders. However, we did not replicate the thinning of RNFL, GCL, and choroid. Higher IL-6, IL-1β, and TNF-α levels were associated with decreased left macular thickness and higher IL-6 was associated with thinning of right IPL and left choroid in the overall sample. Thinning of right IPL and left macula were also associated with worse executive functioning and attention. Another major finding of our study was that patients with schizophrenia had higher proinflammatory cytokine levels compared to healthy controls. These results support the immune hypothesis of schizophrenia and highlight the influence of inflammatory aberrancies in the pathophysiology of the disorder. In patients with schizophrenia, IPL thinning was associated with increased BMI and decreased HDL levels. Moreover, decreased inflammatory response, particularly a decreased TNF-α level, was related to IPL thinning which was at trend level for right IPL but statistically significant for left IPL. A trend-level positive correlation was observed between left IPL thickness and executive functioning score.

Findings from early studies indicating retinal structural changes in patients with schizophrenia suggest that these changes which are rapidly and easily detected by OCT could be potential disease biomarkers. However, there is some inconsistency in the literature. Besides studies reporting that patients did not differ from controls [17, 40], there are also reports of thinning in retinal layers, especially in chronic, treatment-resistant patient groups [33, 34, 37]. Different definitions of patients (disease stage, inclusion of schizoaffective disorder patients, etc.); variation of age, ethnicity, and smoking rates among study groups; the presence of medical comorbidities and utilizing different OCT devices and/or segmentation methods across studies seem to pave the way for the emergence of controversial results in the literature. For instance, Miller et al. (2020) showed an inter-scanner variability with up to 8 μm mean difference for RNFL between two machines [47]. Therefore, before suggesting OCT findings for use as an objective biomarker in schizophrenia, further studies are needed to confirm positive findings in the literature and determine the biological and clinical correlates of observed variations.

In our study conducted based on this point of view, we found that IPL thinning was associated with lower HDL and higher BMI levels in patients. There was an association between worse metabolic profile and thinning of other retinal layers both in patients and in the overall sample, i.e., a positive correlation between HDL and right RNFL and negative correlations between glucose and right GCL and BMI and right macula. Trend-level observations were also in the same direction except for the association observed between right choroid and BMI. These findings suggest that medical comorbidities which are overexpressed in schizophrenia, such as metabolic syndrome may affect retinal layer thicknesses. Support for this comes from the study by Silverstein et al. (2018) reporting that thinning of retinal layers was observed only in patients with comorbid diseases such as diabetes and hypertension, and those without comorbidities did not differ from controls [40]. More recently, in a small sample, Bannai et al. (2020) found that having cardiometabolic disorders had a significant impact on total retinal thickness with some trending effects for inner plexiform and outer nuclear layers [41]. Studies in the general population also indicate the effect of metabolic conditions on retinal thicknesses. New et al. (2021) showed that patients with MetS had significant thinning in RNFL and macular thicknesses with an elevated triglycerides level being an independent risk factor for inferior parafoveal macula thinning [48]. A meta-analysis of studies evaluating OCT findings in obesity showed an overall trend of decreasing retinal thicknesses in high BMI patients, with temporal RNFL and nasal choroidal thickness showing statistical significance [49]. A RNFL thinning has been reported in patients with insulin resistance [50] and RNFL and GCL + IPL thicknesses have been found decreased in diabetic patients with no retinopathy [51]. However, results are more conflicting for central choroidal thickness. Wong et al. (2013) found that subfoveal choroidal thickness was significantly higher in subjects with hypercholesterolemia [52]. In our study, although the mean fasting glucose level was higher in the patients, the groups were well matched in terms of other metabolic syndrome-related parameters, such as BMI, fasting lipid levels, and smoking status. These parameters were not evaluated in most of the previous OCT studies and, thus, inconsistent findings in the literature might be due to differences in the distribution of these comorbidities among study groups. Given that metabolic syndrome risk is increased by two-to-threefold in schizophrenia compared to healthy population [53], metabolic syndrome-related conditions, such as impaired lipid profile and increased BMI levels, may explain at least some of the OCT abnormalities reported in patients.

An association between schizophrenia and the immune system is increasingly recognised and supported by epidemiological and genetic studies [9, 54, 55]. The coincidence of various central structural alterations and high proinflammatory cytokine levels in schizophrenia suggests that inflammatory mechanisms may be involved in the occurrence of these alterations. Based on this, we investigated the relationship between retinal structural variations and proinflammatory cytokine levels in schizophrenia. First of all, we found that all three cytokine levels were highly elevated in patients compared to controls after controlling for confounding factors, such as age, gender, BMI, metabolic parameters, and smoking status. These findings support the role of the immune system in the pathophysiology of the disorder. With regards to the role of immune mediators on OCT findings in psychotic disorders, Liu et al. (2020) found that increased CNTF levels, a neurotrophic factor that plays a nutritional and regulatory role in retinal cells and a member of IL-6 cytokine family, were associated with decreased total RNFL thickness in both eyes of patients [42]. However, no studies have been published so far investigating the relationship between OCT findings and proinflammatory cytokine levels in neuropsychiatric disorders. In terms of the general population, a higher baseline IL-6 level was found associated with thinner macular GC-IPL at follow-up in the middle-aged adult cohort [56] and an increased serum IL-6 level was associated with foveal inner plexiform layer thinning in HIV-infected children [57]. We found that left macular thinning was associated with an increase in all proinflammatory cytokine levels in the overall sample, and increased IL-6 level was associated with decreased right IPL and left choroidal thicknesses. An inverse correlation between IL-6 levels and left choroidal thickness was also evident in the patient group, whereas thinning of IPL was related to lower TNF-α levels. It is not clear why IL-6 and TNF-α affect retinal thicknesses in opposite directions in patients with schizophrenia; however, one possible explanation of this observation might be the different effects of those cytokines on the permeability of the blood-retinal barrier (BRB). In animal models, it has been shown that TNF-α injection increases the permeability of BRB, whereas IL-6 injection causes no measurable changes [58]. Increased vascular permeability and cellular infiltration may lead to an increase in retinal layer thicknesses or at least may be masking a possible thinning of those layers which could be expected due to degenerative effect of chronic inflammation. Therefore, our results indicating a significant association of increased IPL thickness with higher TNF-α level may be representative of this situation. Similar results have been found in a study investigating the relationship between inflammatory markers and CNS alterations. Lizano et al. (2021) showed that increased TNF-α level was associated with increased right medial orbital frontal and middle temporal cortex thicknesses and left thalamic volume in psychosis probands, whereas there was an inverse correlation between IL-6 level and left pars orbitalis and right superior temporal sulcus thickness in healthy controls [59]. However, further studies are crucial for a better understanding of the role of immune aberrations and the differential effects of cytokines on retinal structural alterations. Moreover, it is not clear why the effect was observed in some layers with no relation with others.

In terms of disease-related clinical parameters, we did not find an association between retinal thicknesses and disease severity. This is consistent with the findings of most studies in the literature. While no significant correlation was found in previous studies investigating the relationship between global RNFL thickness and disease severity [17, 33, 41], the results for GCL and IPL are more controversial with some reporting no association and others reporting an inverse correlation [37, 41]. Concerning the relationship between disease duration and OCT parameters, disease duration was positively correlated with right GCL and right and left IPL thicknesses in our sample which is not consistent with the previous findings. Most of the studies in the literature indicated either a negative correlation between the duration of disease and retinal thicknesses or no relation at all. More recently, Alizadeh et al. (2021) showed that longer disease duration was associated with thicker RNFL in acute patients, while in chronic patients, an opposite association was observed [60]. All these studies have a cross-sectional design and long-term studies investigating retinal thicknesses in the course of disease could shed light on the relationship between disease duration and retinal structural alterations. Higher mean daily CPZe doses were associated with thinning of right GCL, right choroid, and left RNFL in our sample. These findings are in line with the known functional and trophic effects of dopamine in the retina [61]. Boudriot et al. (2022) reported that higher CPZe doses were associated with lower parafoveal macular and macular RNFL thicknesses [62], although there are some studies with negative results in the literature as well [38, 40].

Previous studies investigating the relationship between retinal structural changes and cognitive functions have mostly focused on dementia and MS patients. Data come from these studies show that OCT variations are correlated with MRI findings and both RNFL and GC-IPL thicknesses are associated with cognitive performance [27, 63, 64]. However, the results of early studies investigating the relationship between OCT changes and cognitive functions in psychotic disorders are controversial [36, 41, 42]. In these studies, either a brief assessment tool or a single specific test has been used for measuring cognition. Here, we utilized a comprehensive battery of neuropsychological tests to be able to evaluate cognitive subdomains in detail. We only found a trend-level observation between left IPL and executive functioning compound score in patients. In terms of the individual subscale scores, a significant positive correlation has emerged between immediate memory score and RNFL and choroidal thicknesses in both eyes. In the overall sample, executive functioning was significantly correlated with both eye IPL and macular thicknesses. Attention compound score was also correlated with IPL and macular thicknesses with being statistically significant in right IPL and left macula. These findings suggest that retinal thicknesses, especially IPL, may reflect cognitive functioning. However, given that comorbid conditions frequently observed in schizophrenia, such as increased inflammatory response and metabolic diseases, affect retinal layer thicknesses in different directions and that these comorbidities have also been related to the level of cognitive impairment [11, 53, 65], it is difficult to establish a direct association between cognition and OCT findings in schizophrenia patients.

Higher cytokine levels were associated with worse cognitive functioning in the overall sample which is most possibly driven by the disease effect. All three cytokine levels were significantly correlated with executive functioning, attention, and memory scores. There was no significant association between compound cognitive scores and any of proinflammatory cytokines in patients; however, higher CRP level was correlated with worse executive functioning. In the previous studies, increased CRP levels have been found associated with impairment of working memory, mental flexibility, processing speed, memory, and visual attention [66, 67]. Contrarily, we found that higher IL-1β and IL-6 levels were associated with better cognitive functioning in healthy controls. This could be explained by the positive effects of proinflammatory cytokines on brain functions at normal concentrations. Studies show that cytokines modulate brain development, long-term potentiation, synaptic functions, and neurotransmission in physiological conditions [67, 68].

Our findings indicating side-specific alterations in retinal layer thicknesses and different correlation patterns between eyes could resemble cerebral lateralization of the brain in terms of volume, functionality, and connectivity. Asymmetrical changes observed in our study are in line with previous OCT studies of schizophrenia [41, 60, 69]. Post hoc analyses revealed that left and right eye asymmetry was less prominent in schizophrenia patients in comparison to controls which may reflect abnormal brain lateralization reported in schizophrenia [70, 71].

We recognize several limitations to our investigation. First, our priori power analysis was based on RNFL. Therefore, the sample size might have been relatively small to detect a significant difference between study groups for some of the comparisons. Therefore, our findings should be replicated in larger samples. Second, the duration of illness is relatively large, daily mean CPZe doses are high, and total PANSS score is low in our population which may restrict the generalizability of our results. Third, we did not correct for multiple comparisons because of the exploratory nature of the study. Moreover, comparisons were not independent, since the inherent correlation of retinal thicknesses between and within regions. Finally, all patients were on various antipsychotic medications at the time of the study and a significant association was observed between CPZe dose and thinning of some retinal layers. Therefore, it is not possible to disregard the effect of antipsychotic drugs on retinal thinning. Future investigations including patients at various disease stages with different clinical characteristics, particularly those including drug naïve first-episode patients, are highly warranted. Our previous study indicating an IPL thinning in unaffected first-degree relatives of schizophrenia patients supports the idea that retinal thinning observed in patients is rather a representative of underlying disease mechanism and cannot be solely explained by the effects of antipsychotic medications or metabolic conditions [72].

In conclusion, our findings indicate a significant thinning of right IPL in patients with schizophrenia after controlling for various confounders including cardiometabolic factors. The IPL layer consists of ganglion cell dendrites and synaptic connections. A thinning in the IPL layer might be a proxy for the abnormal synaptic organization of neurons in schizophrenia. We did not replicate the results of studies in the literature showing the thinning of other retinal layers, such as RNFL, GCL, and choroid in a sample with a high inflammatory response. Our results show that abnormal inflammatory response, which is observed in around 38% of schizophrenia patients [73], may have some effect on retinal thicknesses and confirmed the contribution of the metabolic state of the subjects on OCT findings. Even that differences observed in retinal thicknesses seem to be rather small to be clinically meaningful or serve as a biomarker for schizophrenia [20], considering the common embryological development of the retina and brain, and observed correlation between cognitive functioning and retinal thicknesses, further OCT studies would be useful to shed light on neuropathological mechanisms involved in the development of disorder. For this purpose, studies investigating OCT changes in samples that are less likely to be affected by disease-related confounders, such as first-episode drug naïve patients or clinical high-risk individuals, are highly warranted.

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Data availability The data that support the findings of this study are not openly available and are available from the corresponding author upon reasonable request.

Declarations

Conflict of interests All other authors declare that they have no conflicts of interest.

Ethical approval The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki) and approved by the local research ethics committee. All participants provided informed written consent for the study.

References

1. Keefe RS, Fenton WS (2007) How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr Bull 33(4):912–920
2. Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET (2000) Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157(1):16–25
3. Shenton ME, Dickey CC, Frumin M, McCarley RW (2001) A review of MRI findings in schizophrenia. Schizophr Res 49(1–2):1–52
4. Lawrie SM, Abukmeil SS (1998) Brain abnormality in schizophrenia: a systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry 172(2):110–120
5. Antonova E, Sharma T, Morris R, Kumari V (2004) The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res 70(2–3):117–145
6. Sahbaz C, Zibandey N, Kurtulmus A, Duran Y, Gokalp M, Kırpınar I, Sahin F, Guloksuz S, Akkoc T (2020) Reduced regulatory T cells with increased proinflammatory response in patients with schizophrenia. Psychopharmacology:1–11
7. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B (2011) Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiat 70(7):663–671
8. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E (2008) Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiat 63(8):801–808
9. Ripke S, Neale BM, Corvin A et al (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511(7510):421–427. https://doi.org/10.1038/nature13595
10. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB (2015) Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. The Lancet Psychiatry 2(3):258–270
11. Fillman S, Weickert T, Lenroot R, Catts S, Bruggemann J, Catts V, Weickert C (2016) Elevated peripheral cytokines characterize a subgroup of people with schizophrenia displaying poor verbal fluency and reduced Broca's area volume. Mol Psychiatry 21(8):1090
12. Papiol S, Molina V, Desco M, Rosa A, Reig S, Gispert JD, Sanz J, Palomo T, Fananás L (2005) Ventricular enlargement in schizophrenia is associated with a genetic polymorphism at the interleukin-1 receptor antagonist gene. Neuroimage 27(4):1002–1006
13. Meisenzahl EM, Rujescu D, Kirner A, Giegling I, Kathmann N, Leinsinger G, Maag K, Hegerl U, Hahn K, Möller H-J (2001) Association of an interleukin-1β genetic polymorphism with altered brain structure in patients with schizophrenia. Am J Psychiatry 158(8):1316–1319
14. Hoseth EZ, Westlye LT, Hope S, Dieset I, Aukrust P, Melle I, Haukvik U, Agartz I, Ueland T, Ueland T (2016) Association between cytokine levels, verbal memory and hippocampus volume in psychotic disorders and healthy controls. Acta Psychiatr Scand 133(1):53–62

15. Miller B, Mellor A, Buckley P (2013) Interleukin-6 and cognition in non-affective psychosis. Schizophr Bull 39:S242–S243
16. Joe P, Ahmad M, Riley G, Weissman J, Smith RT, Malaspina D (2018) A pilot study assessing retinal pathology in psychosis using optical coherence tomography: Choroidal and macular thickness. Psychiatry Res 263:158–161
17. Chu EM-Y, Kolappan M, Barnes TR, Joyce EM, Ron MA (2012) A window into the brain: an in vivo study of the retina in schizophrenia using optical coherence tomography. Psychiatry Research: Neuroimaging 203(1):89–94
18. London A, Benhar I, Schwartz M (2013) The retina as a window to the brain—from eye research to CNS disorders. Nat Rev Neurol 9(1):44
19. Sahbaz C, Elbay A, Ozcelik M, Ozdemir H (2020) Insomnia Might Influence the Thickness of Choroid, Retinal Nerve Fiber and Inner Plexiform Layer. Brain Sci 10(3):178
20. Kazakos CT, Karageorgiou V (2020) Retinal Changes in Schizophrenia: A Systematic Review and Meta-analysis Based on Individual Participant Data. Schizophr Bull 46(1):27–42. https://doi.org/10.1093/schbul/sbz106
21. Lizano P, Bannai D, Lutz O, Kim LA, Miller J, Keshavan M (2020) A Meta-analysis of Retinal Cytoarchitectural Abnormalities in Schizophrenia and Bipolar Disorder. Schizophr Bull 46(1):43–53. https://doi.org/10.1093/schbul/sbz029
22. Vujosevic S, Parra MM, Hartnett ME, O'Toole L, Nuzzi A, Limoli C, Villani E, Nucci P (2022) Optical coherence tomography as retinal imaging biomarker of neuroinflammation/neurodegeneration in systemic disorders in adults and children. Eye (Lond):1–17. doi:https://doi.org/10.1038/s41433-022-02056-9
23. Frohman EM, Fujimoto JG, Frohman TC, Calabresi PA, Cutter G, Balcer LJ (2008) Optical coherence tomography: a window into the mechanisms of multiple sclerosis. Nat Rev Neurol 4(12):664
24. Schneider E, Zimmermann H, Oberwahrenbrock T, Kaufhold F, Kadas EM, Petzold A, Bilger F, Borisow N, Jarius S, Wildemann B (2013) Optical coherence tomography reveals distinct patterns of retinal damage in neuromyelitis optica and multiple sclerosis. PLoS ONE 8(6):e66151
25. Roth NM, Saidha S, Zimmermann H, Brandt AU, Isensee J, Benkhellouf-Rutkowska A, Dornauer M, Kühn AA, Müller T, Calabresi PA (2014) Photoreceptor layer thinning in idiopathic Parkinson's disease. Mov Disord 29(9):1163–1170
26. Iseri PK, Altinas Ö, Tokay T, Yüksel N (2006) Relationship between cognitive impairment and retinal morphological and visual functional abnormalities in Alzheimer disease. J Neuroophthalmol 26(1):18–24
27. Siger M, Dzięgielewski K, Jasek L, Bieniek M, Nicpan A, Nawrocki J, Selmaj K (2008) Optical coherence tomography in multiple sclerosis. J Neurol 255(10):1555–1560
28. Liu D, Zhang L, Li Z, Zhang X, Wu Y, Yang H, Min B, Zhang X, Ma D, Lu Y (2015) Thinner changes of the retinal nerve fiber layer in patients with mild cognitive impairment and Alzheimer's disease. BMC Neurol 15(1):14
29. Ong Y-T, Hilal S, Cheung CY, Venketasubramanian N, Niessen WJ, Vrooman H, Anuar AR, Chew M, Chen C, Wong TY (2015) Retinal neurodegeneration on optical coherence tomography and cerebral atrophy. Neurosci Lett 584:12–16
30. Mutlu U, Bonnemaijer PWM, Ikram MA, Colijn JM, Cremers LGM, Buitendijk GHS, Vingerling JR, Niessen WJ, Vernooij MW, Klaver CCW, Ikram MK (2017) Retinal neurodegeneration and brain MRI markers: the Rotterdam Study. Neurobiol Aging 60:183–191. https://doi.org/10.1016/j.neurobiolaging.2017.09.003
31. Mutlu U, Colijn JM, Ikram MA, Bonnemaijer PWM, Licher S, Wolters FJ, Tiemeier H, Koudstaal PJ, Klaver CCW, Ikram MK (2018) Association of Retinal Neurodegeneration on Optical Coherence Tomography With Dementia: A Population-Based Study. JAMA Neurol 75(10):1256–1263. https://doi.org/10.1001/jamaneurol.2018.1563
32. Cabezon L, Ascaso F, Ramiro P, Quintanilla M, Gutierrez L, Lobo A, Cristobal J (2012) Optical coherence tomography: a window into the brain of schizophrenic patients. Acta Ophthalmologica 90
33. Lee WW, Tajunisah I, Sharmilla K, Peyman M, Subrayan V (2013) Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: evidence from optical coherence tomography. Invest Ophthalmol Vis Sci 54(12):7785–7792
34. Ascaso FJ, Rodriguez-Jimenez R, Cabezón L, López-Antón R, Santabárbara J, De la Cámara C, Modrego PJ, Quintanilla MA, Bagney A, Gutierrez L (2015) Retinal nerve fiber layer and macular thickness in patients with schizophrenia: Influence of recent illness episodes. Psychiatry Res 229(1–2):230–236
35. Pan J, Zhou Y, Xiang Y, Yu J (2018) Retinal nerve fiber layer thickness changes in Schizophrenia: A meta-analysis of case–control studies. Psychiatry Res 270:786–791
36. Liu Y, Chen J, Huang L, Yan S, Bian Q, Yang F (2021) Relationships Among Retinal Nerve Fiber Layer Thickness, Vascular Endothelial Growth Factor, and Cognitive Impairment in Patients with Schizophrenia. Neuropsychiatr Dis Treat 17:3597–3606. https://doi.org/10.2147/ndt.S336077
37. Celik M, Kalenderoglu A, Karadag AS, Egilmez OB, Han-Almis B, Şimşek A (2016) Decreases in ganglion cell layer and inner plexiform layer volumes correlate better with disease severity in schizophrenia patients than retinal nerve fiber layer thickness: Findings from spectral optic coherence tomography. Eur Psychiatry 32:9–15
38. Samani NN, Proudlock FA, Siram V, Suraweera C, Hutchinson C, Nelson CP, Al-Uzri M, Gottlob I (2017) Retinal layer abnormalities as biomarkers of schizophrenia. Schizophr Bull 44(4):876–885
39. Gonzalez-Diaz JM, Radua J, Sanchez-Dalmau B, Camos-Carreras A, Zamora DC, Bernardo M (2022) Mapping Retinal Abnormalities in Psychosis: Meta-analytical Evidence for Focal Peripapillary and Macular Reductions. Schizophr Bull. https://doi.org/10.1093/schbul/sbac085
40. Silverstein SM, Paterno D, Cherneski L, Green S (2018) Optical coherence tomography indices of structural retinal pathology in schizophrenia. Psychol Med 48(12):2023–2033
41. Bannai D, Lizano P, Kasetty M, Lutz O, Zeng V, Sarvode S, Kim LA, Hill S, Tamminga C, Clementz B (2020) Retinal layer abnormalities and their association with clinical and brain measures in psychotic disorders: A preliminary study. Psychiatry Research: Neuroimaging:111061
42. Liu Y, Huang L, Tong Y, Chen J, Gao D, Yang F (2020) Association of retinal nerve fiber abnormalities with serum CNTF and cognitive functions in schizophrenia patients. PeerJ 8:e9279. doi:https://doi.org/10.7717/peerj.9279
43. Heaton RK (1981) Wisconsin card sorting test manual; revised and expanded. Psychological Assessment Resources:5–57
44. Golden CJ, Freshwater SM (1978) Stroop color and word test.
45. Oktem O (1992) A verbal test of memory processes: a preliminary study. Archives of Neuropsychiatry 29(4):196–206
46. Reitan RM (1992) Trail Making Test: Manual for administration and scoring. Reitan Neuropsychology Laboratory,
47. Miller M, Zemon V, Nolan-Kenney R, Balcer LJ, Goff DC, Worthington M, Hasanaj L, Butler PD (2020) Optical coherence tomography of the retina in schizophrenia: Inter-device agreement and relations with perceptual function. Schizophr Res 219:13–18. https://doi.org/10.1016/j.schres.2019.10.046
48. New SH, Leow SN, Vasudevan SK, Idris IB, Tang SF, Din NM (2021) Relationship between anthropometric and biochemical changes of metabolic syndrome with retinal nerve fiber layer and macular thickness. PLoS One 16 (2):e0246830. doi:https://doi.org/10.1371/journal.pone.0246830

49. Salehi MA, Karimi A, Mohammadi S, Arevalo JF (2022) Spectral-domain OCT measurements in obesity: A systematic review and meta-analysis. PLoS One 17 (4):e0267495. doi:https://doi.org/10.1371/journal.pone.0267495
50. Uzun F, Fındık H, Polat HB (2019) The evaluation of retinal nerve fiber layer thickness in subjects with insulin resistance. Pamukkale Tıp Dergisi 12(3):503–508
51. Rodrigues EB, Urias MG, Penha FM, Badaró E, Novais E, Meirelles R, Farah ME (2015) Diabetes induces changes in neuroretina before retinal vessels: a spectral-domain optical coherence tomography study. International Journal of Retina and Vitreous 1(1):1–8
52. Wong RL, Zhao P, Lai WW (2013) Choroidal thickness in relation to hypercholesterolemia on enhanced depth imaging optical coherence tomography. Retina 33(2):423–428
53. Bora E, Akdede B, Alptekin K (2017) The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis. Psychol Med 47(6):1030–1040
54. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, Tooley K, Presumey J, Baum M, Van Doren V (2016) Schizophrenia risk from complex variation of complement component 4. Nature 530(7589):177–183
55. Eaton WW, Byrne M, Ewald H, Mors O, Chen C-Y, Agerbo E, Mortensen PB (2006) Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. Am J Psychiatry 163(3):521–528
56. Paulsen AJ, Pinto A, Merten N, Chen Y, Fischer ME, Huang GH, Klein BEK, Schubert CR, Cruickshanks KJ (2021) Factors Associated with the Macular Ganglion Cell-Inner Plexiform Layer Thickness in a Cohort of Middle-aged U.S. Adults. Optom Vis Sci 98 (3):295–305. doi:https://doi.org/10.1097/opx.0000000000001650
57. Blokhuis C, Doeleman S, Cohen S, Demirkaya N, Scherpbier HJ, Kootstra NA, Kuhle J, Teunissen CE, Verbraak FD, Pajkrt D (2017) Inflammatory and Neuronal Biomarkers Associated With Retinal Thinning in Pediatric HIV. Invest Ophthalmol Vis Sci 58(13):5985–5992. https://doi.org/10.1167/iovs.17-22252
58. Bamforth S, Lightman S, Greenwood J (1996) The effect of TNF-α and IL-6 on the permeability of the rat blood-retinal barrier in vivo. Acta Neuropathol 91(6):624–632
59. Lizano P, Lutz O, Xu Y, Rubin LH, Paskowitz L, Lee AM, Eum S, Keedy SK, Hill SK, Reilly JL, Wu B, Tamminga CA, Clementz BA, Pearlson GD, Gershon ES, Keshavan MS, Sweeney JA, Bishop JR (2021) Multivariate relationships between peripheral inflammatory marker subtypes and cognitive and brain structural measures in psychosis. Mol Psychiatry 26(7):3430–3443. https://doi.org/10.1038/s41380-020-00914-0
60. Alizadeh M, Delborde Y, Ahmadpanah M, Seifrabiee MA, Jahangard L, Bazzazi N, Brand S (2021) Non-linear associations between retinal nerve fibre layer (RNFL) and positive and negative symptoms among men with acute and chronic schizophrenia spectrum disorder. J Psychiatr Res 141:81–91. https://doi.org/10.1016/j.jpsychires.2021.06.007
61. Witkovsky P (2004) Dopamine and retinal function Documenta ophthalmologica 108(1):17–39
62. Boudriot E, Schworm B, Slapakova L, Hanken K, Jäger I, Stephan M, Gabriel V, Ioannou G, Melcher J, Hasanaj G, Campana M, Moussiopoulou J, Löhrs L, Hasan A, Falkai P, Pogarell O, Priglinger S, Keeser D, Kern C, Wagner E, Raabe FJ (2022) Optical coherence tomography reveals retinal thinning in schizophrenia spectrum disorders. Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-022-01455-z
63. Choi SH, Park SJ, Kim NR (2016) Macular Ganglion Cell -Inner Plexiform Layer Thickness Is Associated with Clinical Progression in Mild Cognitive Impairment and Alzheimers Disease. PLoS ONE 11(9):e0162202–e0162202. https://doi.org/10.1371/journal.pone.0162202
64. Stellmann JP, Cetin H, Young KL, Hodecker S, Pöttgen J, Bittersohl D, Hassenstein A, Oberwahrenbrock T, Heesen C, Siemonsen S (2017) Pattern of gray matter volumes related to retinal thickness and its association with cognitive function in relapsing–remitting MS. Brain and behavior 7(2):e00614
65. Ribeiro-Santos R, Lucio Teixeira A, Vinicius Salgado J (2014) Evidence for an immune role on cognition in schizophrenia: a systematic review. Curr Neuropharmacol 12(3):273–280
66. Bulzacka E, Boyer L, Schürhoff F, Godin O, Berna F, Brunel L, Andrianarisoa M, Aouizerate B, Capdevielle D, Chéreau-Boudet I, Chesnoy-Servanin G, Danion JM, Dubertret C, Dubreucq J, Faget C, Gabayet F, Le Gloahec T, Llorca PM, Mallet J, Misdrahi D, Rey R, Richieri R, Passerieux C, Roux P, Yazbek H, Leboyer M, Fond G (2016) Chronic Peripheral Inflammation is Associated With Cognitive Impairment in Schizophrenia: Results From the Multicentric FACE-SZ Dataset. Schizophr Bull 42(5):1290–1302. https://doi.org/10.1093/schbul/sbw029
67. Misiak B, Stańczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D (2018) Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: A systematic review. Schizophr Res 192:16–29. https://doi.org/10.1016/j.schres.2017.04.015
68. Avital A, Goshen I, Kamsler A, Segal M, Iverfeldt K, Richter-Levin G, Yirmiya R (2003) Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. Hippocampus 13(7):826–834. https://doi.org/10.1002/hipo.10135
69. Schönfeldt-Lecuona C, Kregel T, Schmidt A, Kassubek J, Dreyhaupt J, Freudenmann RW, Connemann BJ, Gahr M, Pinkhardt EH (2020) Retinal single-layer analysis with optical coherence tomography (OCT) in schizophrenia spectrum disorder. Schizophr Res 219:5–12
70. Ribolsi M, Daskalakis ZJ, Siracusano A, Koch G (2014) Abnormal asymmetry of brain connectivity in schizophrenia. Front Hum Neurosci 8:1010
71. Ocklenburg S, Güntürkün O, Hugdahl K, Hirnstein M (2015) Laterality and mental disorders in the postgenomic age–A closer look at schizophrenia and language lateralization. Neurosci Biobehav Rev 59:100–110
72. Kurtulmus A, Elbay A, Parlakkaya FB, Kilicarslan T, Ozdemir MH, Kirpinar I (2020) An investigation of retinal layer thicknesses in unaffected first-degree relatives of schizophrenia patients. Schizophrenia Research
73. Zhang Y, Catts V, Sheedy D, McCrossin T, Kril J, Weickert CS (2016) Cortical grey matter volume reduction in people with schizophrenia is associated with neuro-inflammation. Transl Psychiatry 6(12):e982