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Review

THE USE OF ELECTRORETINOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH SCHIZOPHRENIA

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SUMMARY – The use of electroretinography (ERG) and optical coherence tomography (OCT) has currently expanded beyond ophthalmology alone. The aim of this review is to present the results and knowledge acquired by these two methods in patients suffering from schizophrenia. Reviewing the studies applying ERG and OCT methods in the field of psychiatry, one can conclude that results of the research imply morphological and functional changes of retina in patients with schizophrenia that are not consistent. However, in most studies there was reduction of the amplitude and changes in the implicit time related parameters on ERG and thinning of the retinal nerve fiber layer on OCT. Neurons in the eye use the same neurotransmitters as neurons in the basal brain structures that are most affected in schizophrenia, according to the dopamine hypothesis of schizophrenia. Unlike neurons in the basal brain structures, the neurons in the eye are *in vivo* available to ERG. Using the aforementioned tests together with clinical diagnostic criteria of schizophrenia, the subgroups with different prognostic and therapeutic specificities within schizophrenia as a group of diseases might be identified more precisely.

Key words: *Schizophrenia; Electroretinography; Optical coherence tomography; Neuroophthalmology*

Introduction

Schizophrenia is one of the 15 most common diseases that lead to disability and working incapacity[1]. In Croatia, there are more than 18,000 (registered) patients with schizophrenia, and 1,000 are hospitalized on a yearly basis[2]. Since schizophrenia begins slowly, with gradual onset of symptoms, it often remains unrecognized and untreated for a certain period of time[3]. The period during which the patient manifests symptoms of the disease and has not been treated is called duration of untreated psychosis (DUP)[4]. It has been proven that the sooner psychopharmacotherapy, psychotherapy and sociotherapy is started, the better is prognosis of the disease. Therefore, early detection of the disease is of crucial importance for long-term prognosis and favorable outcomes of the disease[5]. Studies have shown that early intervention in healthy individuals at a high risk of disease development may reduce the incidence of comorbidities such as depressive thoughts, suicide attempts, and can generally prolong duration of remission of positive and especially negative symptoms[5,6]. Interventions consist of the use of antipsychotics, but also other drugs, as well as various psychotherapeutic and sociotherapeutic techniques. Although reduction in the duration of DUP proved useful, it did not reduce the incidence of the disease[6].

The disease usually starts between the ages of 18 and 22, and the occurrence of the disease is equal in

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both genders[1]. We still do not have clear pathoanatomic, pathophysiologic and etiologic criteria for definition of the disease. In other words, we are missing a clear biologic marker. Therefore, at present, the diagnosis of schizophrenia is still made solely based on clinical findings and according to the currently used diagnostic, symptom-based criteria.

None of the currently available laboratory and physical (imaging) tests provides pathognomonic finding for schizophrenia. New studies on electroretinography (ERG) and optical coherence tomography (OCT) have opened the door to the research of the central nervous system in living patients with schizophrenia. Namely, the retina is an integral part of the central nervous system and is derived from the same tissue as the telencephalon, i.e. the ectoderm. It does not contain myelin and is available to visualization and investigation *in vivo* by noninvasive methods. The axons of the retinal ganglion cells form the optic nerve through which the signal is passed to the central nervous system. Thus, there is a premise for investigating nervous system in living patients, with the possibility of defining specific biologic indicators of schizophrenia by noninvasive methods such as ERG and OCT.

The light passes through the cornea and the lens, then through the vitreous body to the retina. In the retina, it first passes through the ganglion cells, then through the layers of the nuclei of the amacrine, bipolar and horizontal cells before reaching a layer of photoreceptors located on the outer part of the retina. There are two types of photoreceptors, i.e., rods (for black and white viewing and viewing in the dark) and cones (for viewing colors and viewing in the light conditions). Photochemical substances are found in the outer section of the photoreceptor, which are rhodopsin in the rods and different types of photopsin in the cones (selective sensitivity for red, blue or green, which is the basis of color vision).

From the photoreceptors, the signal is transmitted across horizontal and bipolar cells to ganglion cells and through the optic nerve, and visual pathways ending in the visual cortex located in the occipital lobe. When the rods are exposed to light, the resulting receptor potential is different from the receptor potentials in almost all other sensory receptors. It increases the negativity of membrane potential, causing hyperpolarization. Under normal conditions when the photoreceptor is not stimulated, the electrical potential is -40 mV, and at maximum stimuli hyperpolarizes it to -80 mV. The conduction of most of the signals in the retina neurons occurs electrotonically. Electrotonic conduction, unlike an action potential, is a direct flow of electrical current in the neuron cytoplasm and in the axons from the site of stimulation to the synaptic output.

The retina is particularly interesting for investigations into neurophysiology because many of its cells produce neurotransmitters. For example, photoreceptors produce glutamate and amacrine cells produce at least eight types of neurotransmitters including GABA, glycine, dopamine, acetylcholine and indolamine. Retinal ganglion cells produce glutamate, somatostatin and substance P[7]. Today, the applicability of ERG and OCT has extended beyond its use exclusively in ophthalmology. *In vivo* biologic indicators associated with schizophrenia are of great importance in studies of the pathogenesis, screening, and early diagnosis of disease, as well as the course of disease and response to treatment[7].

The aim of this review is to present the results and knowledge in this area acquired by the application of ERG and OCT in schizophrenic patients.

Electroretinography

Electroretinography is a noninvasive diagnostic method that measures the outbreaks of electrical potential that arise in response to light in different cells within the retina. It is used in ophthalmology to diagnose retinal disease (e.g., retinal dystrophies). The signals that arise are generally of low intensity and are measured in nanovolts (nV) or microvolts (mV). There are several types of ERG: flash ERG (fERG), full field ERG (ffERG), multifocal ERG (mfERG) and pattern ERG (pERG).

The electrical potential generated by light stimulation consists of the negative a-wave, which reflects hyperpolarization of the photoreceptors, positive b-wave that represents depolarization of bipolar and Müller cells in the retina, and c-wave as a positive wave that arises in response to stimulation of the pigment layer and the rods. Photopic negative response (phNR) is the negative potential that follows b-wave, and is created by ganglion cells. It occurs only in fERG testing. ERG records the amplitude of the individual waves, the implicit time (time from light stimulation to the peak amplitude of waves) and latency (time from the

onset of stimulus to the onset of wave). Photopic vision is vision in bright light conditions, which is necessary for color perception. Cone photoreceptors have the main role in recognizing this type of stimulation. Scotopic conditions are adaptation of vision in darkness, when rods are activated. Changes in the photoreceptor function were recorded in the study by Warner *et al.*[8]. They analyzed ERG findings in nine patients with schizophrenia and nine healthy subjects, and showed changes in photoreceptor function in patients suffering from schizophrenia. Decreased amplitudes of a-waves were identified in patients regardless of the dose of antipsychotics. The authors attributed these results to the absence of omega-3 fatty acids in the cell membrane of the retinal photoceptor, which caused impaired perception of light, as previously reported from the study by Horrobin *et al.*[9]. The study was conducted consequently to the research by Marmor *et al.*, where difference in electrical potential between patients with schizophrenia and control group was not demonstrated[10]. The investigation by Warner *et al.*[8] was inspired by the observation reported by Gerbaldo *et al.*[11] in patients with schizophrenia who had a tendency of 'photophilic activity' (staring at the Sun) and reduced sensitivity to light, with lower amplitudes of b-wave on ERG. Holopigian *et al.* examined the effect of the dopaminergic receptor blocker on the characteristics of fERG. The results showed a decrease in the b-wave amplitude without changing the implicit time[12].

Balogh *et al.* conducted studies on a sample of 63 middle aged subjects (26 patients with schizophrenia, 17 with bipolar affective disorder, and 20 healthy subjects as a control group), aiming to analyze light processing in the acute stage of the afore-mentioned diseases using the ERG method[13]. The findings revealed a decrease in the a-wave amplitudes in photopic conditions only in patients in the acute phase of schizophrenia, and negative correlation between a-wave amplitudes and positive symptoms (using the Positive and Negative Syndrome Scale (PANSS) questionnaire). Negative symptoms, as well as the duration of treatment and doses of antipsychotics were not correlated with ERG indicators. The abnormality of the wave depended on the stage of the disease because normalization of the wave was observed after decrease of symptom intensity. Namely, after eight-week follow up and reduction in the intensity of positive symptoms of schizophrenia, there were no significant differences between patients with schizophrenia and control group. ERG abnormalities were not found in the bipolar disorder group.

Hébert *et al.* found deviation from the normal findings for young, healthy individuals at a high risk of developing schizophrenia or bipolar affective disorder using ERG[14]. In their study, population at a high risk of developing schizophrenia was defined as having positive psychiatric heredity (one parent suffering from schizophrenia or bipolar disorder or multi-generation heredity for these disorders). The study included 58 subjects, i.e., 29 subjects with positive heredity and 29 healthy controls without any known psychiatric heredity. Studies in the scotopic conditions recorded a significantly reduced b-wave amplitude in the high-risk group after correction for age, gender, season at the time of testing and heredity, either for schizophrenia or bipolar affective disorder[14]. This research is particularly important because it suggests that this method can serve as an early and specific biomarker for the risk of developing these mental illnesses and may contribute to the noninvasive, rapid and simple screening, early treatment initiation, and more favorable disease outcomes[14]. According to the concept of early interventions (within a period of up to 5 years from the onset of the disease), it is known that when the treatment is started earlier, better long-term outcomes can be achieved in terms of remission, recovery, and patient functionality.

Unlike Balogh *et al.*[13], who found a reduced a-wave amplitude in patients with schizophrenia, Hébert *et al.*[14] did not prove this. Researchers believe that the results varied due to a large sample of subjects with bipolar disorder heredity in the study by Hébert *et al.*[14]. The same researchers later confirmed reduction of a-wave amplitudes in photopic conditions and reduction of b-wave amplitudes in scotopic conditions in adult patients with schizophrenia, as indicated in their earlier study on healthy subjects at a high risk of developing the disease. This was an ERG study with the largest sample to date (105 patients and 150 healthy controls)[15].

A group of American researchers used a RETeval ERG device (LKC Technologies, Gaithersburg, MD, USA) to compare findings in 25 patients with schizophrenia and 25 healthy adult subjects[16]. Individuals with retinal diseases that could affect normal function-

Table 1. Electroretinography (ERG) research in psychiatric patients

Authors	Year	Patients	Healthy subjects	Mean age (yrs)	Medication	Comorbidities that cause retinal changes	PANSS	Results
Warner *et al.*[8]	1999	9 (Sch)	9	/	Chlorpromazine or none	/	/	Decreased a-wave amplitudes in photopic and scotopic conditions in patients regardless of medication
Gerbaldo *et al.*[11]	1992	9 (Sch)	13	37.5	Haloperidol	/	/	Decreased b-wave amplitudes in 'photophilic' Sch group (n=6) during scotopic testing
Holopigian *et al.*[12]	1994	/	19	26.7	Chlorpromazine, Fluphenazine Metoclopramide	/	/	Decreased b-wave amplitudes while on chlorpromazine and fluphenazine medication, but without changes while using metoclopramide in scotopic and photopic flicker tests
Balogh *et al.*[13]	2008	26 (Sch) 17 (BAD)	20	38.2	Sch: olanzapine, risperidone, quetiapine, clozapine, BAD: olanzapine, valproate, lithium, clonazepam, citalopram	/	Yes	Patients with Sch in the acute stage showed decreased a-wave amplitudes (in correlation with positive symptoms) using flash ERG testing, while participants with bipolar disorder did not show ERG anomalies
Hébert *et al.*[14,15]	2010	29 (Sch and BAD)	29	20.7	/	/	/	Decreased b-wave amplitudes in participants at a high risk of developing Sch and BAD, tested in scotopic conditions
Demmin *et al.*[16]	2018	25 (Sch)	25		Antipsychotics	Excluded	Yes	Correlation of negative symptoms and decrease in a-wave amplitude on photopic testing (P_{PhNR}) and correlation of excitement with longer b-wave implicit time in scotopic conditions (S2)

ERG= electroretinography; yrs = years; PANSS = Positive and Negative Syndrome Scale questionnaire; Sch = schizophrenia; BAD = bipolar affective disorder; P_{PhNR} = photopic testing

ing of the retina were not involved in the study. The PANSS questionnaire was used to evaluate the severity of symptoms in patients with schizophrenia in the past two weeks.

The advantage of the RETeval ERG device is that it does not require dilation of the pupil or direct contact with the cornea. The device uses troland (Td) illuminance that measures, adjusts to pupil size, and adjusts the intensity of brightness accordingly to ensure that a constant number of photoreceptors is stimulated at any time. Subjects were investigated under photopic (cone activation) and scotopic (rod activated) conditions.

In the first photopic test (P1), a 100 Td·S repetitive flash stimulation of 1 Hz frequency was used without background light. In the next photopic test (P2), stimulation with a flash of 100 Td·S with background of 340 Td·S under higher frequency (2 Hz) was used, and in the third (P_{PhNR}) test, red light of 58 Td·S with blue background of 380 Td·S with an even higher frequency (3.4 Hz) to trigger reaction of ganglion cells was used. The last photopic test was the Pf-flicker test that uses light flashing of 85 Td·S at a frequency of 28.3 Hz to record the response of bipolar cells (used in psychiatric studies for the first time). The scotopic tests consisted of white flashes of 2.8 Td·S with a frequency 0.25 Hz for S1 test, 28 Td·S 0.1 Hz for S2 test and 280 Td·S with a frequency of 0.05 Hz for S3 test. All the scotopic tests were performed without background light.

In the group of patients with schizophrenia, the results showed that a-wave had a decreased amplitude in photopic tests P1 and P_{PhNR}, while b-wave had a decreased amplitude in P1 and P2 tests. The a-wave also had a decreased amplitude in S3, while a decreased amplitude of b-wave was found in S2 and S3 tests. Longer latency time of b-wave was observed in P2. In scotopic conditions, the implicit time for a-wave and b-wave was longer. Pf-flicker test showed a decrease in wave amplitude in the patient group. P_{PhNR} test showed a decrease in the wave negativity 72 ms after stimulation.

Correlation of the results on PANSS was significant for the following parameters: negative symptoms with decreased a-wave amplitudes (photopic P_{PhNR} test) and b-wave (scotopic) and with longer implicit time of a-wave (scotopic S1 test); negative symptoms with reduction of PhNR amplitude 72 ms after stimulus; and excitement symptoms with longer implicit time in b-wave (S2). However, after false discovery rate corrections, statistically significant remained the correlation of negative symptoms with a-wave amplitudes during photopic testing (P_{PhNR}), and correlation of excitement symptoms with the implicit time of b-wave in the scotopic conditions (S2). No correlation was demonstrated between the dose of antipsychotic pharmacotherapy and retinal response. Researchers believe that the correlation of negative symptoms and weakened response of the retina (reduced ERG amplitude) to stimulation could indicate the same neurotransmitter pathophysiology based on the neurotransmitter hypothesis of schizophrenia, especially the dopaminergic hypothesis[16].

The results of these studies examining the characteristics and changes of ERG (a-wave and b-wave amplitudes and implicit time) in patients with schizophrenia and the association of reductions in wave amplitudes and changes of implicit time in correlation with stages of the disease are shown in Table 1. These results show a significant role of the ERG method in the investigation of pathophysiology of psychiatric disorders, especially schizophrenia and bipolar disorder. Furthermore, it is a noninvasive method, which is well tolerated by adults and children, patients and control group subjects. Further research should focus on better defining these indicators and examining the possible mechanisms underlying the ERG changes observed.

Optical Coherence Tomography

Optical coherence tomography is a diagnostic method that uses low coherence light waves to create a high-resolution cross section image of the retina (1-10 μm). The device creates a picture by measuring the echo time delay of the light and intensity of the reflected light.

Coherence represents two waves that have a constant phase difference in the stage and the same frequency. A tomogram is a two-dimensional image that depicts the intersection of a three-dimensional image; by combining multiple tomograms, we get a three-dimensional display. The advantage of the OCT is that it is a noninvasive and noncontact method that shows the real time condition and *in vivo*. Other advantages are that the examination price is relatively low, it is fast, and there is no contraindication for the application of this diagnostic technique.

The device first came into use in medicine in the early 1990s, and was used primarily in ophthalmology, to get an insight into the morphology of the posterior segment of the eye, usually for analysis of the morphology of the macula and the papilla of the optic nerve. It allows measurements of certain structures and possible pathologic changes in them, such as glaucoma, diabetic maculopathy and retinopathy, age-related macular degeneration, macular rupture and pseudorupture, central serous maculopathy and epiretinal membranes[17]. Today, its usefulness is recognized in other medical specialties, e.g., in interventional cardiology as a useful supplementary diagnostic device in percutaneous coronary interventions (PCI)[18], in dermatology in the diagnosis of non-melanoma skin tumors and other inflammatory skin diseases[19], and in neurology where signs of some diseases can be found in the retina (in Alzheimer's disease, Parkinson's disease, multiple sclerosis)[20]. Thinning of the retinal nerve fiber layer (RNFL) has been demonstrated in patients with optic neuritis, multiple sclerosis, mild cognitive disorders[21], and in patients with Alzheimer's disease[22], where it correlates with the severity of cognitive deficits.

Optical coherence tomography imaging in psychiatric research including patients suffering from schizophrenia began with Chu *et al.*[23]. These authors conducted and published the first study of retinal changes using an OCT device in patients with schizophrenia and schizoaffective disorder. The study included 49 patients and 40 healthy controls. Out of 49 patients, 38 were diagnosed with schizophrenia and 11 with schizoaffective disorder. Forty patients had been prescribed antipsychotics, 10 antidepressants, four mood stabilizers along with antipsychotics, two only mood stabilizers, one had been prescribed hypnotic, and five patients were medication free. Control group consisted of 40 healthy age- and gender-matched individuals. Comparison of retinal thickness indicators between the groups was conducted using statistical multilevel analyses. Patients with schizoaffective disorder were found to have thinner RNFL in the right nasal quadrant compared to people with schizophrenia, and the severity of positive symptoms was associated with a lower macular volume. This study was limited by low resolution of the OCT device[23].

Samani *et al.* used Leica Envisu TM SD-OCT high resolution device to analyze changes in macula and fovea[24]. They examined 85 participants (35 diagnosed with schizophrenia and 50 healthy control subjects). The PANSS questionnaire was used to evaluate the severity of symptoms in patients. The macula and the fovea (located inside the macula) are particularly interesting in research since it is the site of the sharpest vision dominated by photoreceptors (cones) and ganglion cells.

The device was used to measure thickness of the following: RNFL; ganglion cell layer (GCL); inner plexiform layer (IPL); inner nuclear layer (INL); outer plexiform layer (OPL); outer nuclear layer (ONL); inner segmented layer (ISL); outer segmented layer (OSL); cone outer segment tips (COST); and retinal pigment epithelium (RPE). The derived measures included thickness of the following: whole retina = RNFL-RPE; photoreceptor complex = ONL-COST; processing/processing complex = RNFL-OPL; and ganglionic cell complex = GCL+IPL. Sensitivity to contrast was also measured in 44 patients and 44 controls (selected depending on their Freiburg Acuity Test results) and showed spherical equivalent to be lower in patients. The results showed significant reduction in thickness of the photoreceptor complex in all regions, thinning of the OPL and ISL in patients with schizophrenia. In addition, reduction of contrast sensitivity was correlated with thinning of the temporal parafoveal ganglion cell complex. The severity of negative symptoms was negatively correlated with thickness of the foveal photoreceptor complex and ONL.

Ascaso *et al.* examined 30 patients with schizophrenia and 30 healthy controls[25]. The subjects were examined by Time Domain OCT (TD-OCT) to establish differences between the groups regarding the existence of a recent psychotic episode in the last month (recent illness episode, RIE) or the last six months (non-recent illness episode, NRIE) in relation to control. The incidence and intensity of symptoms were evaluated by the PANSS questionnaire. All patients were treated with antipsychotics. Since this device does not adjust to the pupil size, the pupils were dilated with 1% tropicamide. Thickness of the RNFL, thickness of the macula and macular volume were measured. All patients were found to have thinning of the peripapillary RNFL in all quadrants of both eyes. Macular thickness and macula volume were also reduced in all patients in both eyes. Thickness of the macular inner ring, foveal thickness, and the volume of macula of the left eye were statistically significantly re-

duced. Comparison of the two patient subgroups (RIE and NRIE) yielded significant differences in the above-mentioned characteristics compared to the control group, which were mainly identified in NRIE patients. The authors claim that inflammation could be the reason why a significant difference was not found in the RIE subgroup, i.e., inflammatory processes increase thickness of the human retina, as previously shown by Stock *et al.*[26]. Inflammatory processes have been described in patients with schizophrenia, during acute episodes of schizophrenia, both in the first psychosis episode and in chronic patients[27,28]. With the use of multivariate regression models and after correction for age, no significant link was found in this study between duration of the disease and thickness of the peripapillary RNFL, macular thickness and macular density either in all subjects or in patient subgroups[26].

Scientists from Kuala Lumpur examined the use of SD-OCT to analyze RNFL changes in patients with schizophrenia and their association with the duration of the disease[29]. The intensity of symptoms was assessed following the DSM-IV diagnostic criteria and using the PANSS questionnaire. Patients (N=30) with schizophrenia were divided into subgroups of acute, chronic and long-term chronic patients, and compared to 30 healthy age-, gender- and race-matched subjects. OCT was used to measure thickness of the peripapillary RNFL, average thickness of the macula, and volume of the macula. Since there were no differences between the left and right eye, further research was continued solely examining the right eye of the subjects. Differences were found in RNFL thickness between patients and healthy subjects. In patients with schizophrenia, significant differences in RNFL thickness were found in the peripapillary area of the retina in the superior, inferior and temporal quadrant, but not in the nasal quadrant. Significantly thinner macula in general, as well as thinning of the central part of the macula, inner and outer ring of the macula in patients compared to controls was also identified. When the inner and outer rings were divided into quadrants, a significant difference between the groups was demonstrated in all quadrants. The volume of the macula was also reduced in patients. The RNFL size and reduction in the volume of the macula were more significant in long-term chronic patients and were significantly related to the duration of the disease. Such results indicate the value of the OCT method applied in monitoring of disease progression. However, correlation of the obtained parameters with rating of the PANSS questionnaire was not demonstrated. The authors attributed these results to the neurodegenerative nature of the disease and to neurochemical dysregulation[27]. It has been demonstrated that the dopamine neurotransmitter system plays a major role in visual functions such as contrast sensitivity and color perception[30]. Contrast sensitivity and color perception are affected in diseases with dopaminergic issues such as Parkinson's disease, but also in schizophrenia[31]. Therefore, thinning of the RNFL has been attributed to the possible dopamine dysregulation[24,25].

Using the same method, Yilmaz *et al.*[32] found statistically significant thinning of the RNFL also in the nasal quadrant in patients compared to healthy subjects. They analyzed the findings using SD-OCT in 34 patients with schizophrenia and 30 healthy individuals to determine changes in RNFL thickness. Thickness of the macula in the nasal quadrant and the inferior outer quadrant was also significantly thinner in patients. The average macular thickness and thickness of the macula in superior external, superior internal, temporal external and temporal internal, nasal internal and inferior interior quadrants were all reduced, but not significantly. The researchers attributed these changes to the neurodegenerative nature of schizophrenia.

Silverstein *et al.*[33] examined the influence of comorbidities in patients with schizophrenia on the results obtained using SD-OCT. Compared to the group of healthy subjects, there were no differences in RNFL thickness, macula and inner nuclear layer, and the determined thinning of the retinal structures was associated with diseases such as diabetes mellitus and arterial hypertension in both groups of subjects. The study showed changes in the optic nerve head in patients with schizophrenia. The study also found an increase in cup-to-disc ratio of the optic nerve papilla, which was independent of comorbidities. Such results indicate the need for further research of the optic nerve head changes as a possible biomarker of schizophrenia.

Joe *et al.*[34] also investigated the use of SD-OCT in pursuit of biomarkers in psychosis. They studied macular thickness and were among the first who studied thickness of the vascular layer supplying the retina, i.e., choroid. Six chronic psychiatric patients were involved (three with schizophrenia and three with bipolar disorder) and 18 healthy age- and gender-matched con-

Table 2. Optical coherence tomography (OCT) research in patients with schizophrenia

Authors	Year	Patients	Healthy participants	Mean age (yrs)	Medication	Comorbidities that can cause retinal changes	PANSS	Results
Chu *et al.*[23]	2012	38 (Sch) 11 (schizoaffective disorder)	49	29.7	40 used antipsychotics, 4 used mood stabilizers + antipsychotics, 2 used mood stabilizers, 1 used nocturnal sedation, 5 non-medicated	Excluded	/	Thinning of RNFL in all patients Patients with schizoaffective disorder had thinner RNFL in right nasal quadrant compared to patients with schizophrenia
Samani *et al.*[24]	2017	35 (Sch)	50	40.6	Antipsychotics	/	Yes	Patients showed thinning of photoreceptor complex in all regions, thinning of outer plexiform layer and inner segmented layer Decreased contrast sensitivity correlated with thinning of temporal parafoveal complex of ganglion cells The severity of negative symptoms was negatively related to thickness of foveal photoreceptor complex and outer plexiform layer
Ascaso *et al.*[25]	2015	20 (NRIE) (Sch) 10 (RIE) (Sch)	30	44.8	Antipsychotics	Excluded	Yes	All patients showed thinning of peripapillary RNFL in all quadrants of both eyes Macular thickness and macular volume were also decreased in all patients in both eyes Decreased macular inner ring, foveal thickness and macular volume in the left eye were statistically significant
Lee *et al.*[29]	2013	30 (Sch)	30	35.07	Antipsychotics	Excluded	Yes	Thinning of RNFL in the peripapillary area of the retina in superior, inferior and temporal quadrants in patients Thinning of the central part of the macula, inner and outer macular ring, as well as macular volume decrease were found in patients The amount of RNFL thinning and decrease of macular volume correlated with disease duration
Yilmaz *et al.*[32]	2015	34 (Sch)	30	39.22	/	Excluded	/	Thinning of RNFL in patients in all quadrants Macular thickness in nasal quadrant and inferior outer quadrant was also significantly thinner
Silverstein *et al.*[33]	2018	32 (Sch)	32	40.9	Antipsychotics	/	Yes	The patient group showed enlarged cup volume and enlarged cup-to-disc ratio in both eyes These findings were unrelated to medical comorbidity and were related to cognitive symptoms

OCT = optical coherence tomography; yrs = years; PANSS = Positive and Negative Syndrome Scale questionnaire; Sch = schizophrenia; RIE = recent illness episode; NRIE = non-recent illness episode; RNFL = retinal nerve fiber layer

trols. As in previous studies, they found thinning of the macula, especially the inner ring of the macula (statistically significant), which they attributed to neurodegenerative changes. They also found thinning of the choroid in the individuals with psychosis, but it was not statistically significant, which they attributed to a small sample of study participants. The authors indicate the need for further research of these changes and their association with inflammation and degenerative changes of the central nervous system.

From the above, we can conclude that the majority of studies using the OCT in patients with schizophrenia determined thinning of the RNFL (Table 2). These results are undermined by methodologic limitations of the studies, such as relatively small samples and comorbidities (e.g., diabetes and arterial hypertension) with possible influences on the retinal structures examined.

Conclusion

Reviewing the research regarding the application of ERG and OCT methods in the field of psychiatry, one can conclude that the results of research conducted imply morphological and functional changes in patients with schizophrenia that are not consistent. However, in most studies, there was reduction in the amplitude and changes in the implicit time related parameters in the ERG, and thinning of the RNFL in the OCT. Further, especially longitudinal prospective research is needed to define specific biologic indicators using these methods for the purpose of early screening, diagnostics and monitoring of patients in certain stages of the disease, and for therapeutic response in patients. There is an obvious need for longitudinal prospective research in order to define specific biologic indicators using these methods for the possible early screening, differential diagnosis, monitoring of relapse and therapeutic response of patients in specific stages of the disease. The neurons in the eye are available *in vivo*, and they use the same neurotransmitters as the neurons in the basal brain structures that are most affected in schizophrenia according to the dopamine hypothesis of schizophrenia. The use of ERG and OCT, along with the established clinical diagnosis of schizophrenia can help define clear subgroups within schizophrenia as a group of diseases according to ERG and OCT findings. These subgroups would have different prognostic and therapeutic specificities[35,36]. We can also expect a clear and defined biologic marker that would increase the accuracy of the disease diagnosis and enable early initiation of treatment.

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Sažetak

PRIMJENA ELEKTRORETINOGRAFIJE I OPTIČKE KOHERENTNE TOMOGRAFIJE U BOLESNIKA SA SHIZOFRENIJOM

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Primjena elektroretinografije (ERG) i optičke koherentne tomografije (OCT) danas nadilazi primjenu isključivo u oftalmologiji. Cilj ovoga pregleda je prikazati rezultate i spoznaje dobivene primjenom ovih metoda u shizofrenih bolesnika. Pregledom dosadašnjih istraživanja primjene metoda ERG-a i OCT-a u području psihijatrije možemo zaključiti da rezultati provedenih istraživanja morfoloških i funkcionalnih promjena retine u bolesnika sa shizofrenijom nisu konzistentni. Ipak, u većini istraživanja nalaze se smanjenje amplituda i promjene implicitnog vremena u ERG-u te stanjenje sloja mrežničnih živčanih vlakana na OCT-u. Kako se radi o neuronima dostupnima *in vivo* koji koriste iste neurotransmitere kao i neuroni u središnjim strukturama mozga koji su po dopaminskoj hipotezi shizofrenije najzahvaćeniji, primjenom spomenutih pretraga uz uobičajenu dijagnostiku shizofrenije možemo očekivati definiranje jasnijih podskupina unutar shizofrenije kao skupine bolesti koje bi imale različite prognostičke i terapijske specifičnosti.

Ključne riječi: *Shizofrenija; Elektroretinografija; Optička koherentna tomografija; Neurooftalmologija*