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Mini review article

STRUCTURAL RETINAL ABNORMALITIES AS POTENTIAL MARKERS FOR PSYCHOSIS SPECTRUM DISORDERS

STRUKTURNE RETINALNE ABNORMALNOSTI KAO POTENCIJALNI MARKERI ZA POREMEĆAJE IZ PSIHOTIČNOG SPEKTRA

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Abstract

Retinal nerve structures are the only part of central nervous system where neurons can be observed directly, *in vivo*. In the recent years, advances have been made in retinal imaging. Some of this progress is due to use of optical coherence tomography scanners, common in ophthalmological clinical practice. Today, this method provides high precision in the visualization of retina, providing close to an "optical biopsy" of distinct retinal layers. Identification of biological markers that have diagnostic or therapeutic value in psychosis spectrum disorders is one of the most important tasks for current neurobiological research. Recently, new evidence for reduction of retinal structures, such as retinal nerve fiber layer and ganglionic cell thickness in schizophrenia, has emerged. In the present article, evidence on retinal thinning in schizophrenia and related disorders is summarized and discussed. However, the current evidence is conflicting, owing to both the heterogeneity of the disorder, and the methodological differences of the described studies.

Keywords:
psychosis,
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Sažetak

Retinalni neuronski spletovi su jedini deo centralnog nervnog sistema gde se neuroni mogu vizuelizovati direktno, in vivo. Tokom poslednjih godina metode vizuelizacije retine značajno su napredovale. Tomografija optičke koherencije je jedna od savremenih metoda koja se često upotrebljava u rutinskoj oftalmološkoj praksi. Ova metoda danas obezbeđuje visoku preciznost prilikom vizuelizacije retine, omogućavajući "optičku biopsiju" pojedinih retinalnih slojeva. Identifikacija bioloških markera koji imaju dijagnostički ili terapijski značaj za poremećaje iz psihotičnog spektra predstavlja jedan od ključnih zadataka za savremenu nauku. Nedavno su pokazana umanjenja debljine pojedinih struktura retine u poremećajima iz psihotičnog spektra, poput umanjenja debljine vlakana retinalnog živca, kao i umanjenja debljine sloja retinalnih ganglijskih ćelija. U ovom preglednom članku sumirane su najznačajnije studije o strukturnim izmenama retine u shizofreniji i povezanim poremećajima. Zaključeno je da su postojeći dokazi o postojanju strukturnih promena retine u psihozi kontradiktorni, kako zbog metodoloških razlika u dosadašnjim studijama, tako i usled heterogenosti samog poremećaja.

Ključne reči:
psihoza,
retina,
tomografija optičke koherence,
shizofrenija

Retina – a window into the brain

Poets and philosophers have defined eyes as a window into the soul. In the scientific communication, for a long time retina has been considered as "a window into the brain". Today, modern science has found concrete biological reasons for the use of such a poetic metaphor. Namely, the nerve structures that comprise retinal layers are the only part of the central nervous system (CNS) where nerve structures can be observed directly, *in vivo*. Retinal neural axons are non-myelinated, i.e. they are not concealed by the thick myelin sheaths, characteristic for many other nerve structures across the CNS. These non-myelinated cells are also not concealed by the skull, thus making the retina a unique model for the direct examination of neural structures.

Axons of retinal ganglion cells converge on the optic disc, where the optic nerve is formed. Then, a further path is formed by connecting to the lateral geniculate body of the thalamus and to the superior colliculus in the midbrain. Projections from these centers are relayed at the primary visual cortex of the occipital lobe. Complex visual information is then processed to the associative visual cortical centers in the adjacent occipital lobe (1).

Significance for schizophrenia

Schizophrenia is a major psychiatric disorder that involves distinct, diverse and functionally different brain areas. After decades of research, it has become apparent that a single, unitary "lesion" of this polygenic and multifactorial complex disorder does not exist. Nowadays, according to the well-known and widely accepted hypothesis, schizophrenia is conceptualized as a neurodevelopmental disorder, in which the complex interaction between genetic load, specialization and development of different brain areas, and the increasing demands of the environment results in the visible clinical manifestations of the disorder during adolescence or in early adulthood (2,3). In parallel, a neurodegenerative aspect of the disorder has been consistently described (since the introduction of the idea by Kraepelin in the beginning of the 20th century) (4) and still cannot be ruled out, at least in a proportion of cases (5). The neurodegenerative component of the disorder was proven by a progressive decline in affective, cognitive and behavioral functional aspects, as patients advanced into the older age (6,7).

Reception and integration of sensory input originating from the external world is the foundation of meaningful experiences. One of the hallmarks of psychotic spectrum disorders, including schizophrenia as its most prominent representative, are perceptual distortions. A whole spectrum of perceptual impairments has been observed in psychosis, ranging from slight symptoms in prodromal phases of the disorder (8), and its attenuated forms (9), to full blown hallucinatory experiences (hallucinations - perceptions without stimulus) - acoustic hallucinations in particular. Perceiving sounds and voices without auditory stimulus is highly prevalent in psychosis. Whether the affected individuals will or will not have insight into the hallucinations depends on many factors. Nevertheless, a person with insight will report less interference with daily activities than a person with no insight (5).

The importance of visual distortions in psychosis spectrum disorder also captured the attention of influential thinkers such as Jung (10). He theorized that these disturbances signified a fundamental disturbance of the patients relationship with its surroundings, graphically illustrating the isolation that menaces him (11). Recent evidence even challenges the traditional views that visual hallucinations (VHs) are atypical or uncommon in psychosis. The weighted mean for VHs is 27% in schizophrenia, 15% in affective psychosis, and 7.3% in the general community (12). These forms of perceptual distortions are linked to a more severe psychopathological profile and less favorable outcome in psychosis. Furthermore, in people at high risk of psychosis development (13), visual abnormalities may indicate transition from - at risk state (sub-threshold, non-clinical phenomenology) to -

full blown psychosis episode (14).

Higher prevalence of perceptual disturbances is accompanied by paranoid ideation. This is well documented in people suffering from progressive loss of one of the sensory modalities (i.e. vision, hearing, etc.) (15). Thus, slight changes in the visual sensorium bear significance for the experience of psychosis. Interestingly, there are no described cases of schizophrenia in people who are suffering from congenital blindness (16,17). Thus, a question arises - does the inactivity of the retina serve as a protective factor against the disorder? In absence of other notable evidence, drawing specific conclusions is impossible without more scientific data on the relation between the eye and schizophrenia.

One of the most significant findings in the history of schizophrenia research is the discovery of antipsychotic medication, followed by the dopaminergic theory of schizophrenia. Furthermore, in the last few decades, the glutamatergic theory has become largely influential (18). The retina is rich in both D1 and D2 family of receptors, and dopamine is considered to be a major retinal transmitter. Furthermore, glutamate is the principal excitatory neurotransmitter, with retinal neurons having both the metabotropic and ionotropic glutamate receptors identified (19). Thus, investigating retinal tissue could provide a new opportunity for researching the specific molecular changes associated with schizophrenia.

By tremendous improvement in ophthalmological non-invasive diagnostic (particularly retinal structural imaging) and many potentially intriguing but unanswered questions, in relation to schizophrenia, the time has come to open a new venue of schizophrenia research – the examination of the retinal structures.

Optical coherence tomography - technical aspects

Currently, diverse methods are available for the measurement of both structural and functional aspects of the retinal tissue. Some of the most notable are optical coherence tomography (OCT), retinal vasculature measurements and electroretinography. The focus of this mini-review will be the application of retinal structural imaging in schizophrenia and other psychotic disorders, as measured by optical coherence tomography (20).

Optical coherence tomography is a non-invasive, laser imaging technique. It has significantly influenced the ophthalmological clinical practice, and opened up new areas of understanding, especially in the area of glaucoma, macular degeneration and diabetic retinopathy (21,22). This method delivers high resolution cross-sectional images of the retinal layer structures. Concisely, the light travelling from a broadband light source is divided into a reference beam and a sample beam and directed to the retina. The light from the sample beam reflects back onto the reference beam after hitting the retinal structures. The pattern that results from the interference of echoes between the two beams creates a measurement of light echoes versus depth (22,23).

In the last few years, significant advances in the OCT methodology have been made, and current OCT systems can provide axial resolution of less than 5 μm. Images provided with OCT scanners are highly reproducible, owing to their considerably high resolution and providing close to an in-vivo 'optical biopsy' of the retina (22). The parameters accessible by OCT scanning are given in **Table 1**. Given measures encompass the structural overlay of the retinal tissue.

Retinal structural changes in psychotic disorders

Research of retinal structure changes in psychosis is a relatively new. First reports on the use of OCT in patients with psychosis date as recently as 2010's. Different groups around the world used this approach to look at retinal nerve tissue, from the UK (25,26), Malaysia (27), Turkey (28,29), Spain (30) and USA (31). In the present section, retinal structure changes in schizophrenia and psychosis-spectrum disorders will be summarized.

In Malaysia, Lee et al. examined the peripapillary RNFL and MV in patients with schizophrenia (27). This study encompassed 30 adult patients (mean age: 37 ± 11 years) with schizophrenia, matched with the same number of healthy controls. The exclusion criteria were: any retinal pathology, history of hypotensive crisis, history of intracranial or intraorbital space-occupying lesions, diabetes mellitus or myopia > 2.0 diopters. Patients were stratified according to the duration of illness: acute (less than 2 years; n = 5), chronic (2 to 10 years; n = 13) and long-term chronic (more than 10 years; n = 12) group. In patients (all groups combined), significant reductions in the peripapillary RNFL thickness was found. This was true for overall RNFL thickness (patients vs. controls, 94.7 ± 9.8 vs. 103.5 ± 6.5 μm, respectively), and for three quadrants - superior, inferior and temporal (out of four). Macular thickness was significantly lower in the patient group, as well (269.2 ± 12.6 vs. 284 ± 9.76 μm, respectively). However, after stratification, a reduction of RNFL and macular thickness was present only in the chronic and long-term chronic patient groups. Interestingly, the duration of illness inversely correlated with the overall RNFL thickness (r = -0.36), superior quadrant RNFL thickness (r = -0.45) and macular thickness (r = -0.36). No associations were found between the symptoms of psychosis at the time of evaluation (as measured by PANSS) and the aforementioned retinal parameters. One of the limitations of this study was the low number of patients, most notably in the acute patient group. Moreover, the description of equivalent dosages of antipsychotic medication was omitted. As it was mentioned earlier, the distribution and significance of D1 and D2 receptors in the retina suggested that dopamine antagonism medication could influence the given parameters. Furthermore,

Table 1. Descriptions of structural retinal parameters accessible by OCT scanning

Parameter	Description	Measurements
Retinal nerve fiber layer (RNFL)	Axons originating from the Ganglion Cell layer in the retina. Fibers converge on the optic papilla where the layer thickness is greatest. The axons advance from the optic disc as the second cranial nerve - optic nerve.	• Global average thickness (μm) • 90 percent quadrant sector thickness (μm) ▪ superior ▪ nasal ▪ inferior ▪ temporal • 30 percent sector thickness – 12 clock hour positions (μm)
Ganglion Cell (GC) layer	Soma of ganglion cell neurons. Photoreceptors pass information to interneurons, which process it and pass it to the ganglion cells. Thus, ganglion cells make up the final output nerve tissue in the vertebral retina. GC layer thickness was found to be the most sensitive for detection of retinal tissue loss (24).	• Average thickness (μm) • Minimal thickness (μm) • 60 percent sector thickness (μm)
Macular Volume (MV) and thickness	Oval pigmented area on the posterior pole of the eye. It contains the foveola and is responsible for detailed central vision. Macular Volume is captured by scanning the 6x6 mm cube.	• Average thickness (μm) ▪ subcentral field (foveola) ▪ bordering fields • Volume cube (mm^3)

exclusion criteria did not include presence of hypertension as a potential confounding factor. However, the advantage of this study was the use of Cirrus HD-OCT 4000 machine that has been based on the contemporary spectral-domain technology with high axial resolutions, as well as high reproducibility rate. The authors concluded that OCT retinal scanning might be used in the detection of neuronal degeneration, as a marker for the more severe course of the disorder.

In the study of Chu et al. from the UK (25), patients with both schizophrenia (n = 36) and schizoaffective disorder (n = 11), with a relatively recent onset (illness duration 4.4 ± 3.6 years), were examined. Positive and negative symptom severity was available only for 32 of the patients. Exclusion criteria were: actual systemic disease, history of neurological or ophthalmological disease known to affect the visual pathway, high myopia, previous head injury and drug/alcohol dependence. In comparison to controls, the subjects with schizophrenia and schizoaffective disorder did not differ in overall RNFL thickness. However, the right RNFL nasal quadrant of the schizoaffective group (mean 70.45 μm) was thinner than in the schizophrenia group (mean 88.53 μm, p = 0.02). In patients, positive symptom severity was associated with lower MV (β = −0.54, p = 0.02). When only the subgroup of patients with schizophrenia was assessed, this association was even stronger (β = −0.85, p = 0.04). An important point to make, when evaluating the given study, is that the OCT technology used was non-spectral domain imaging, with many fewer axial scans, which lowers the reproducibility of given findings. The authors concluded that RNFL variations were too subtle to be of value as a biological marker for psychosis. However, this conclusion may be premature, considering the use of lower resolution OCT scanner with low sensitivity of axon visualization. The authors also suggest that it is impossible to exclude the potential neuroprotective effects of antipsychotic therapy (second generation), but the dosages were not equivalent across groups in this study, similar to the situation in the study of Lee et al. In summary, the authors suggested that unmyelinated axons, in patients with schizophrenia/schizoaffective disorder, were not disturbed by the disease process.

In the next important study, Ascaso et al. (30) evaluated OCT parameters in relation to the proximity/distance of a psychotic episode. A total of 30 Spanish subjects with schizophrenia were matched with healthy controls by age (average age around 45 ± 11 years) and sex. Recent illness episode group had a psychotic episode in

the month preceding the OCT scan (n = 10), while a non-recent episode group was clinically stable for 6 months (n = 20). The participants were excluded from the study for systemic diseases, history of neurological or ophthalmological diseases and presence of the refractive error of > ±2 diopters. Mean equivalent chlorpromazine dosages for the patients were relatively high (711.6 ± 490.6 mg). In comparison to controls, the patients had decreased overall peripapillary RNFL thickness (103.27 ± 8.99 vs. 95.1 ± 13.4 m, respectively), as well as the superior (127.3 ± 14.4 vs. 114.6 ± 18 μm, respectively) and the inferior quadrant thickness (134 ± 22.3 vs. 121.1 ± 25.3 μm, respectively). Macular volume (6.65 ± 0.6 vs. 6.98 ± 0.4 mm^3, patients vs. controls, respectively) and thickness (254.1 ± 31.3 vs. 275 ± 15.4 μm, respectively) were also reduced in the patient group. Interestingly, no relationship with OCT parameters and illness duration was found, contrary to the previously shown study by Lee et al. Curiously, however, after stratification for recent/non-recent episode patients, retinal thinning and MV reduction was evident only in the non-recent episode patients. Ascaso et al. suggested that the effect of the axonal loss in schizophrenia might be masked by the transient inflammatory state induced by an acute psychotic episode.

Recently, new evidence for structural retinal changes in schizophrenia came from the study of Yilmaz et al. (29). The OCT examination was made in 34 schizophrenia patients (mean age around 40 ± 10 years) and 60 age matched healthy controls. Participants were excluded based on the presence of major retinal pathology, hypertension or diabetes. Reductions in overall and nasal thickness was found in patients in comparison to controls (87.7 ± 7.3 vs. 93.2 ± 7.5 μm, respectively; p = 0.03). Macular thickness did not differ between the patients and controls (261.1 ± 12.9 vs. 262.6 ± 21 μm, respectively). However, this study did not provide information duration of the illness, number of episodes, recent/non-recent episode, etc. Thus, without the possibility of patient stratification based on these parameters, the generalization of given findings has been limited.

A study done by Celik et al. in Turkey (28) is one of the investigations that managed to examine GC layer, in addition to RNFL. The examination of these parameters was possible by using a spectral domain OCT device. As previously mentioned, GC layer has shown better structure-function correlation, in comparison to RNFL (32). Celik et al. examined these parameters in the context of response to antipsychotic medication. Participants were defined as treatment responsive (n = 41, age 36 ± 11 years, duration of illness 14 ± 8 years), treatment refractory (no response to at least two antipsychotic trials; n = 41, age 35 ± 10 years, duration of illness 12 ± 10 years, and were compared to healthy controls (n = 41, age 35 ± 16 years). Exclusion criteria were based on the presence of degenerative neurological, immunological or systemic diseases. When the whole patient group was compared to controls, patients showed lower RNFL thickness in the temporo-superior (p < 0.01) and temporo-inferior zones (p < 0.01), and overall (p < 0.01). GC layer volumes were also reduced, when all patients with schizophrenia were compared to controls (p < 0.01). They had inverse correlations with various markers of an advanced disorder process, such as number of hospitalizations (r = -0.25, p = 0.02) and disease duration (r = -0.28, p = 0.01). On the other hand, only the treatment-refractory patients had reduced macular thickness, compared to controls (229.5 ± 28.9 vs. 249.1 ± 33.3 μm, respectively) and they had lower GC layer volumes, even in comparison to the patients who were treatment-responsive (1.08 ± 0.07 vs. 1.21 ± 0.04 μm, respectively; p < 0.01). The authors suggested that monitoring of the progression of neurodegeneration should be done with prospective analysis of GC layer.

In 2018, Samani et al. examined parafoveolar thickness of multiple retinal layers, using a hand-held OCT device (26). The sample consisted of 35 patients with schizophrenia and 50 healthy controls matched by age (approx. 40 ± 12 years), sex and ethnicity. The chlorpromazine equivalent dosages were in moderate range (387 ± 274 mg). In patients, significant reductions were found in nasal parafoveal RNFL (β = −2.5 ± 1.0 μm, p < 0.01), and temporal parafoveal GC layer (β = −3.9 ± 2.9 μm, p < 0.01). However, by scanning the parafoveolar area, the authors captured the retinal position where thickness of the RNFL is the lowest. Moreover, authors manually segmented the individual layers of retina. These limitations lower the reproducibility and further interpretation of aforementioned findings.

Finally, in a comprehensive study done by Silverstein et al. in 2018, authors addressed many of the methodological limitations present in previously described studies (31). The authors included 32 patients with schizophrenia (mean chlorpromazine dosage - 462 mg) and 32 age and sex matched controls. No significant differences were found between the groups (patient vs. controls), either in RNFL (87.4 ± 20 vs. 89.4 ± 11.7 μm), GC layer (77.4 ± 8.5 vs. 78.9 ± 11.2 μm), MV (9.7 ± 0.8 vs. 10 ± 0.5 mm^3), or macular thickness (270.3 ± 24.5 vs. 279.22 ± 15.94 μm). In addition, one striking result from this paper was the difference between groups in papillary cup volume and cup-to-disc ratio. Greater volume and ratio was found in patients with schizophrenia (0.55 ± 0.1 vs. 0.41 ± 0.2 mm^3, respectively). The significance of this finding is yet to be established.

Since somatic comorbidities as potential confounders were not considered in detail previously, the same authors stratified the groups into patients/controls with no comorbidity (n = 21 in each group), and patients/controls with hypertension or diabetes (n = 11 in each group) and found significant reductions in all of the mentioned parameters in the latter group. None of the previously described studies have specifically controlled for these conditions, as somatic comorbidities were consistently excluded from analyses. However, it is well established that patients suffering psychotic spectrum disorders do have significant somatic comorbidities. As authors note, diabetes and hypertension are over-represented and often untreated in

schizophrenia.

In summary, the current evidence on structural retinal changes in schizophrenia, at the moment, appears conflicting. Due to different approaches in patient stratification, use of OCT technology and various methodological limitations, the current evidence for thinning of retinal structures in schizophrenia is not yet clear.

Retinal structural changes in bipolar disorder, major depression, neurodegenerative and other disorders

Several neurological conditions with marked neurodegenerative components have revealed changes in retinal thickness, similar to the ones previously described. Thinning of specific retinal layers has been noted in Alzheimer's disease (33), multiple sclerosis (34,35), Parkinson's disease (36). Retinal changes in these disorders encompass both global RNFL and GC layer thinning. Interestingly, cup-to-disc ratio is enlarged in both Alzheimer's disease and multiple sclerosis as well (37), similarly to the changes found in schizophrenia by Silverstein et al.

Recently, significant thinning of both RNFL and GC complex has been found in a study examining bipolar patients (38). In another study examining bipolar patients (39), reduction in RNFL was found in all of the quadrants, except in the temporal one. Furthermore, RNFL thinning was connected with the duration of the disease. However, in patients suffering from mild depressive symptomatology, there was no evidence of RNFL thinning. Interestingly, the duration of the latest depressive episode negatively correlates with nasal RNFL quadrant and GC layer thickness.

A recent investigation published in June 2018 in JAMA Neurology, examined over 30,000 healthy participants, prospectively tracing the changes in cognitive functioning, in relation to baseline OCT scans (40). A thinner baseline RNFL was significantly associated with a future cognitive decline. The study showed that participants in the lowest 2 quintiles of RNFL distribution (measured in the outer nasal retinal subfield) had twice the likelihood of developing a decline in cognitive function over a 3-year period. The described study contributed to the evidence that neurodegeneration, as a phenomenon, is at least partially measurable by and predictable by retinal layer thickness.

Conclusion

Since the introduction of contemporary high-resolution OCT scanning of the retina, conflicting evidence about its possible neural reduction in psychotic-spectrum disorders has emerged. The OCT in vivo imaging can provide reproducible, reliable data that could affect individual patient management and prognosis. At present, retinal thickness reduction likely indicates one of three possibilities. The first possibility is that retinal structures become disturbed by the psychotic process and progressively decline in thickness (marking the illness course). The second possibility is that the thinning of the various structures of retina persists and is stable over time, irrespective of the course of the disorder (marking the illness risk). The third possibility is that retinal thinning is due to comorbid medical diseases (i.e. hypertension, diabetes) that are over-represented in people with serious mental illness. Nevertheless, future investigations with longitudinal design, oriented towards various subpopulations (at-risk populations, treatment-refractory population, early vs. late onset population, etc.), will help us reveal the stability, validity and predictive usefulness of structural retinal markers for improved detection and tailored intervention in psychotic spectrum disorders.

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