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### RESEARCH ARTICLE

#### OCT STUDIES IN SCHIZOPHRENIA: CURRENT EVIDENCE AND FUTURE PERSPECTIVES

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#### Abstract

**Background:** Schizophrenia is a detrimental neurodevelopmental disorder that affects nearly 1 % of the population worldwide. Although schizophrenia ranks among the leading causes of global disease-related disability, definitive investigations do not exist for its diagnosis at present. Since the retina is derived from the same neural layer that the brain develops from, OCT imaging of retina can provide valuable information regarding underlying pathology of schizophrenia.

**Objectives:** This review aims at describing the potential relevance of OCT studies 1) in understanding current insights into retinal structural changes in schizophrenia 2) in understanding the relationship between retinal structural alterations and disease progression and chronicity 3) and to determine the potential role of retinal changes as biomarkers of schizophrenia.

**Methodology:** A comprehensive search of databases such as PubMed, Google Scholar and Medline was conducted using the keywords: schizophrenia, retina, OCT and RNFL changes. Relevant articles were identified and their key findings summarized in this review.

**Conclusion:** OCT studies in schizophrenia patients conducted in recent years continue to provide evidence of retinal structural alterations associated with schizophrenia. However, the findings of these studies vary and there is a need to conduct further studies for clarification regarding the subject. The application of OCT and other neuroimaging techniques to correlate retinal structural alterations with schizophrenia may potentially help establish the role of retinal variables as biomarkers for the disease, and may open a gateway for better diagnostic investigations in schizophrenia.

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#### Introduction:-

Schizophrenia is a detrimental neurodevelopmental disorder (Gracitelli et al., 2015), that affects nearly 1 % of the population worldwide (Murray et al., 1996). The onset of schizophrenia usually occurs in late adolescence or early adulthood (van Os and Kapur, 2009). It is mainly identified clinically by positive and negative symptoms as well as cognitive deficits. Positive symptoms of schizophrenia depict an excess or contortion of normal functions such as delusions, hallucinations and disorganized behavior, whereas, negative symptoms reflect attenuation or absence of behaviors related to interest, expression and motivation such as anhedonia, avolition, blunted affect, apathy, and asocial behavior (Correll and Schooler, 2020). However, the symptoms of schizophrenia can vary in presentation and can also change over the course of time, rendering it a clinically diverse and heterogeneous disorder and making

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it difficult to use only symptomatology as the mainstay of screening for schizophrenia (van Os and Kapur, 2009; Demirci and Calhoun, 2009). Although this debilitating mental disorder ranks among the leading causes of global disease-related disability (Mental Health: New Understanding, New Hope, 2001), definitive investigations do not exist for its diagnosis at present. Schizophrenia is considered to be a neurodevelopmental disorder (Fatemi and Folsom, 2009; Rapoport et al., 2005). Also, neuroimaging studies, especially using Magnetic Resonance Imaging (MRI) suggest a reduction in brain volume in schizophrenia patients, particularly in both gray and white matter of brain, when compared with healthy controls (Olabi et al., 2011; Haijma et al., 2012; Glahn et al., 2008; Ellison-Wright and Bullmore, 2010). Therefore, it is safe to say that the decline in brain volume in schizophrenia patients in relation to disease progression indicates the neurodegenerative component of this disease. So, it is a heterogenous disorder and there is a need to study this disease further. Although these studies have given us better insights into understanding the underlying neuropathology of schizophrenia, they have yet not yielded clinically significant biomarkers for the disease. Hence, there is a need to use reliable and easily available tools in order to understand the ongoing clinical phenomenon as well as the associated cognitive decline in schizophrenia.

### **Imaging the Retina - A “Window” To the Brain**

In the field of psychiatry, where diagnosis is mainly established on clinical basis, there is a need to further investigate the brain functions indirectly, in order to understand the underlying pathology of mental disorders. Imaging the retina could potentially act as a “window” to the brain (Chu et al., 2012). The retina, which forms the innermost layer of the eye, is derived from the same neural layer (ectoderm) that the brain develops from (Silverstein and Rosen, 2015). Therefore, it is considered an extension of the central nervous system (CNS). The retina is composed of neuronal cells such as photoreceptor cells and glial cells (Nguyen, Patel and Tadi, 2020). The retina is further subdivided into ten layers.

#### **Retinal Pigment Epithelium (RPE):**

The retinal pigment epithelium (RPE) forms the outer most layer of the retina. It is located adjacent to the choroid layer, between the neural retina and the Bruch membrane. It supports the underlying capillary endothelium by contributing to the blood-retinal barrier and provides support to the photoreceptor layer for pigment production.

#### **Photoreceptor Layer:**

The photoreceptor layer contains the rods and cones. It is sub-divided into inner and outer segment. The inner segment of the photoreceptor layer is densely rich in mitochondria. The outer segment consists of membrane bound discs, which contain the light-sensitive pigments to carry out phototransduction.

#### **External Limiting Membrane (ELM):**

This region contains gap-junctions between photoreceptor cells and Muller cells. The external limiting membrane separates the cell bodies of the rods and cones from the photoreceptor layer.

#### **Outer Nuclear Layer (ONL):**

It contains the cell bodies of the photoreceptors.

#### **Outer Plexiform Layer (OPL):**

It is the region where the axons of the photoreceptor cells synapse with the dendrites of the bipolar cells in the inner nuclear layer.

#### **Inner Nuclear Layer (INL):**

This layer consists of the cell bodies of bipolar cells, horizontal cells, and amacrine cells. The bipolar cells transmit signals from photoreceptor cells to ganglion cells.

#### **Inner Plexiform Layer (IPL):**

In this layer, the axons of bipolar cells synapse with the dendrites of ganglion cells. The amacrine processes also synapse in this layer and act as inhibitory neurons for bipolar and ganglion cells.

#### **Ganglion Cell Layer (GCL):**

This layer contains the cell bodies of the ganglion cells, that project their axons to form the retinal nerve fiber layer (RNFL).

**Retinal Nerve Fiber Layer (RNFL):**

The RNFL contains the axons of the retinal ganglion cells, which eventually combine to form the optic nerve.

**Inner Limiting Membrane (ILM):**

It forms the innermost layer of the retina and protects the RNFL from the vitreous humor.

The macula is the most sensitive area of the retina and is, therefore, responsible for offering highest visual acuity. The center of the macula contains an avascular depression called the fovea, which contains a high density of cones. The region where the axons of the ganglion cells converge to form the optic nerve is known as the optic nerve head (ONH) or the optic disc. Since this area lacks rods and cones, it is also known as the blind spot of the visual field. The optic nerve ultimately carries the visual information collected by the photoreceptor cells to the brain via visual pathway.

The inner layers of retina are supplied by branches of central retinal artery, which travels inside the optic nerve sheath and pierces the eye at the optic disc. The choroid, which is the second major layer of the eye, vascularizes the outer layers of the retina, and is located adjacent to the retinal pigment epithelium (RPE). The central retinal vein travels along the central retinal artery within the optic nerve sheath and acts as the drainage pathway of the retina (Nguyen, Patel and Tadi, 2020).

Since the retina lacks myelin, this means that any change in the retinal nerve fiber layer will reflect axonal damage (Galletta et al., 2011). Therefore, being an outgrowth of the diencephalon, the retina is the only part of the central nervous system (CNS) available for the direct evaluation of the CNS and also considered an ideal structure for conducting studies in the field of neurodegenerative diseases (London, Benhar and Schwartz, 2012; Galletta et al., 2011; Simao, 2013). According to studies conducted in the recent years, schizophrenia has been attributed with deficits in visual processing and perception (Yeap et al., 2008; Butler et al., 2001). Hence, there is a good reason to conduct studies regarding the imaging of retina, in order to understand the relation of retinal structural changes to the advancement of degenerative changes in schizophrenia.

**Overview of Optical Coherence Tomography (OCT)**

Optical Coherence Tomography (OCT) can provide valuable information on the underlying pathology of neurodegenerative diseases with ocular manifestations (London, Benhar and Schwartz, 2012). Most contemporary OCT devices are able to display high-resolution, cross-sectional images of the retina, RNFL and the optic nerve head and give us information about Retinal Nerve Fiber Layer Thickness (RNFL), Macular Volume (MV), Macular Thickness (MT) as well as optic cup to disc (C/D) ratio in a non-invasive manner (Frohman et al., 2008; Huang et al., 1991). The use of OCT in medicine was first described by Huang and colleagues, who examined the peripapillary area of retina and the coronary artery using OCT in order to demonstrate the diagnostic and therapeutic applications of OCT (Huang et al., 1991). OCT was originally used for quantification of RNFL in the eyes of glaucoma patients as compared to subjects with healthy eyes (Huang et al., 1991). Since then, it has been used extensively in early evaluation of structural changes in the retina in neurodegenerative diseases like Parkinson's disease, Multiple Sclerosis (MS), and Alzheimer's Disease (Kiss et al., 2010; Petzold et al., 2010; Lu et al., 2010), suggesting that this technology might also prove useful in understanding other neurodegenerative disorders. OCT studies are of particular interest in neurological diseases with axonal loss (Lamirel, Newman and Biousse, 2009). Researchers have extensively focused on neuroimaging studies in schizophrenia in order to understand the pathology of the disease and develop biomarkers for schizophrenia (Zarogianni, Moorhead and Lawrie, 2013).

Generally, the OCT technique is considered analogous to that of ultra sound imaging (Frohman et al., 2008). Ultrasound (USG) calculates the time delay in sound echoes and translates it into a 2-dimensional (2-D) image. OCT devices utilize a more advanced principle called interferometry (Schmitt, 1999). Through this principle of interferometry, OCT devices generate a 2-D or 3-D image by calculating phase differences in the backscattered or back-reflected light from the sample (Fercher, 2010). Currently, there are two types of OCT devices available: Time Domain OCT (TD-OCT) and Fourier Domain OCT, which include Spectral Domain OCT (SD-OCT) and Swept Source OCT (SS-OCT).

**Time Domain Oct (TD-OCT)**

In Time Domain OCT (TD-OCT), the interferometer uses a low coherence length light emitting source and directs light rays through a beam splitter onto both the sample and the reference mirror. The light is then reflected back

from both the sample and the rotating reference mirror. As the mirror constantly keeps moving, the back reflection of light from the mirror varies in time. The interference from these two light reflections occurs when the reference arm length matches the sample arm length to a light reflecting site within the coherence length (Fercher, 2010). The resulting image is processed into a 2-dimensional (2-D) or 3-dimensional (3-D) cross-sectional view of the tissue (de Boer et al., 2003).

### **Fourier Domain OCT**

Fourier Domain OCT (FD-OCT) devices acquire signal data by utilizing the spectrum of the interfering light beams reflected at the sample and a stationary reference mirror (instead of using a rotating reference mirror as in Time Domain OCT (TD-OCT), through a spectrometer (Fercher, 2010). Currently, two FD-OCT approaches are available, Spectral Domain-OCT (SD-OCT) and Swept Source-OCT (SS-OCT). Both Spectral Domain OCT (SD-OCT) and Swept Source OCT (SS-OCT) use the spectrum of light instead of using time difference to form a scan of the tissue or sample (Schönfeldt-Lecuona et al., 2015). FD-OCT has the advantage of obtaining high-resolution images relatively quickly as compared with TD-OCT (Fercher, 2010).

### **Discussion:-**

#### **OCT Studies In Schizophrenia**

Although researchers have started studying the application of OCT in schizophrenia only recently, multiple studies have reported retinal structural abnormalities in schizophrenia patients as compared with healthy controls. One of the first studies regarding this subject conducted by (Chu et al., 2012) observed reduced macular volume (MV) in relation to increased expression of positive symptoms. Although they did not observe any significant reduction in overall retinal nerve fiber layer thickness (RNFL) and macular volume (MV) in schizophrenic subjects in comparison with control group, the study was conducted using a cross-sectional study design on a smaller group using an older, low resolution OCT technique as compared to the new spectral domain OCT (SD-OCT), which might not have been able to perceive the insubstantial changes present in the retina of diseased individuals during early years of the disease.

Similarly, (Silverstein et al., 2017) also did not observe RNFL and macula thinning in schizophrenia patients after controlling for medical comorbidities such as diabetes and hypertension, thus supporting the view of (Chu et al., 2012). However, they did report enlarged cup volume and enlarged cup-to-disc ratio in schizophrenia patients in relation to the presence of cognitive symptoms.

On the other hand, (Yilmaz et al., 2015) reported reduced overall and nasal RNFL thickness as well as reduced macular thickness in outer nasal and outer inferior macular areas in schizophrenia patients.

Study conducted by (Ascaso et al., 2010) also found an overall reduction of RNFL thickness, which was particularly pronounced in the nasal quadrant, in schizophrenia patients when compared with controls, but did not observe any changes in macular thickness and volume.

In another study from this group, (Ascaso et al., 2015) found significant reduction in RNFL thickness, macular volume (MV) and macular inner ring thickness. They did not observe any association between retinal measurements and duration of illness. Additionally, after separating the patients into recent illness episode (RIE) and non-recent illness episode (NRIE), only NRIE patients demonstrated reduced retinal thickness in all parameters. The authors suggested that this might be due to neuroinflammation and edema that can occur during an acute illness episode and can mask evidence of tissue loss (as in multiple sclerosis) (Kaufhold et al., 2013).

(Lai et al., 2020) also conducted a similar study to see differences in retinal structure between first episode schizophrenia patients and chronic patients. They also observed no change in RNFL thickness in both groups. However, they reported that macular thickness and volume were reduced in chronic schizophrenia patients in comparison with first episode subjects.

(Lee et al., 2013) also determined if the structural RNFL changes in schizophrenia patients were related to the duration of illness using SD-OCT and they also found significant reduction in overall peripapillary RNFL thickness, macula thickness and macular volume (MV), particularly in the chronic phase of the disease and correlated with increased duration of illness.

One explanation to the finding of absence of retinal structural changes in these studies (Ascaso et al., 2015; Lai et al., 2020; Lee et al., 2013) in recent illness episode (RIE) might be that retinal edema, that occurs as a consequence of neuroinflammation during acute illness phase, can mask the evidence of tissue loss (Topcu-Yilmaz, Aydin and Cetin Ilhan, 2018; Kaufhold et al., 2013).

(Celik et al., 2016) investigated RNFL, Ganglion Cell Layer (GCL) and Inner Plexiform Layer (IPL) thickness in treatment refractory and treatment responsive schizophrenia patients with controls and also evaluated correlation between disease severity and OCT measurements. They reported reduced overall RNFL thickness in schizophrenia patients as compared with controls. They observed choroidal thickness to be lower in treatment resistant patients as compared with treatment responsive patients, but did not observe significant difference in choroidal thickness measurements between overall patient and control groups. They also observed reductions in GCL and IPL volumes, and those classified as treatment resistant demonstrated lower GCL and IPL measurements as compared to treatment responsive patients. They also reported correlation between GCL and IPL measurements and disease severity. GCL-IPL changes were also reported by Jerotic et al., 2020 (in addition to reduction in macular volume and macular thickness) (Jerotic et al., 2020).

Another study was conducted by (Topcu-Yilmaz, Aydin and Cetin Ilhan, 2018), to determine RNFL, macular and sub-foveal choroidal thickness (SFCT) in schizophrenia patients using SD-OCT. They observed macular thinning in multiple regions in schizophrenia patients as compared with controls but did not observe any difference between groups in terms of RNFL thickness and choroidal thickness. But since the authors recruited the patients for their study from an inpatient clinic, who were having a recent psychotic episode, they suggested that the RNFL thinning might have been masked by ongoing inflammation, as observed in a previous study conducted by (Ascaso et al., 2015).

One of the only studies to investigate RNFL and its correlation with visual processing deficits was conducted by (Samani et al., 2017). They observed that the retinal layer changes were related to negative symptoms and contrast sensitivity in schizophrenia patients. They also observed reduced macular thickness in diseased individuals. Patients also demonstrated outer nuclear layer (ONL) and inner segment layer (ISL) thinning in multiple regions, in relation with negative symptom severity. Notably, reduced ganglion cell layer thickness in temporal parafoveal region in patients was associated with decreased low spatial frequency contrast sensitivity, which the authors suggest may reflect magnocellular ganglion cell loss throughout disease progression.

(Bannai et al., 2020) used SD-OCT to identify layer differences within the entire retina in Schizophrenia and BPD patients with psychosis, in relation with cognitive decline and symptom severity. They also addressed the effect of confounders such as age, gender, comorbidities, smoking status, body mass index (BMI), visual acuity, and anti-psychotic medications on the retinal measurements. They reported ONL thinning to be correlated with cognitive decline and reduced brain volume. However, they did not find any correlation between ONL and OPL thickness and clinical or functional parameters. (Samani et al., 2017) also reported ONL thinning to be related with negative symptom severity.

(Schonfeldt-Leucona et al., 2020) reported thinning of nearly all retinal layers, particularly for macular thickness, macular volume, RNFL and INL in patients with schizophrenia spectrum disorder (SSD). Moreover, they also found correlation between the duration of illness and RNFL abnormalities.

(Joe et al., 2018) conducted a pilot study to examine choroidal and macular thickness in patients with psychosis (schizophrenia or bipolar disorder) as compared with age and sex matched healthy controls. Although they reported reduced mean choroidal thickness in psychosis patients, this finding was not statistically significant. However, they did report a significant reduction in macular thickness in patients as compared with healthy controls.

(Silverstein et al., 2017) conducted a study to determine the relationship between retinal structural changes in schizophrenia and comorbid medical conditions (e. g diabetes, hypertension). After eliminating age and medical comorbidities as confounding factors, they did not observe any RNFL or macula thinning in schizophrenia patients and control group, in contrast to what was reported in the prior studies. However, the thinning of RNFL, macula and GCL-IPL was related to the presence of comorbidities such as diabetes and hypertension across the sample as a whole. Nonetheless, even after controlling for confounding factors, schizophrenia patients demonstrated enlarged optic cup volumes and cup-to-disc ratios, which were related to increased cognitive symptoms.

(Miller et al., 2020) conducted a study to determine inter-device agreement of OCT data in schizophrenia using Spectralis and Cirrus OCT devices, for both patient and control groups. Schizophrenia patients showed decreased macular volume on both devices, consistent with the findings of some previous studies (Joe et al., 2018, Ascaso et al., 2015, Lee et al., 2013, Samani et al., 2018, Topcu-Yilmaz et al., 2018) but no change in RNFL thickness, when compared with controls. However, the limitation of the study was that it used a small sample, and did not exclude participants with medical comorbidities.

(Liu et al., 2020) conducted a study to determine RNFL changes and their correlation with Ciliary Neurotrophic Factor (CNTF) and cognitive decline in schizophrenia patients. They reported reduction in RNFL thickness, consistent with the findings of previous studies (Samani et al., 2018) and concluded that decline in RNFL thickness was correlated with decline in serum CNTF and prolonged course of schizophrenia.

The first study to determine the retina layer changes in first degree relatives (FDRs) of schizophrenia patients was conducted by (Kurtulmus et al., 2020). They observed significant reduction in IPL thickness in both schizophrenia patients and FDRs as compared with healthy controls. They observed the difference to remain significant even after controlling for confounders such as age, gender, smoking status and the presence of comorbid medical diseases and BMI (body mass index). Their findings suggest that retinal changes might be trait-related and could potentially serve as endophenotype for the early detection of schizophrenia.

### **Conclusion And Future Implications:-**

Although research in establishing retinal structural correlates of schizophrenia has gained momentum only recently, and the findings of studies vary as well, most of the studies concur with retinal structural abnormalities in schizophrenia patients. Although some of the studies did not find any significant RNFL thinning in relation with schizophrenia (Chu et al., 2012; Silverstein et al., 2017), others did report changes in RNFL thickness, particularly in relation to the chronicity of the disease. Most of the studies provided evidence of macular thinning in correlation with disease severity and progression (Chu et al., 2012; Yilmaz et al., 2016; Ascaso et al., 2015; Lai et al., 2020; Lee et al., 2013; Jerotic et al., 2020; Topcu-yilmaz et al., 2018; Samani et al., 2018; Schonfeldt-leucona et al., 2019; Joe et al., 2018; Miller et al., 2020). Therefore, it can be assumed that changes in macular thickness are the most sensitive indicators of retinal structural changes in schizophrenia and further research can help establish the potential role of macular thickness changes as biomarkers of schizophrenia.

Thus, OCT studies of retina in schizophrenia continue to provide evidence that it can be used a promising neuroimaging technique for schizophrenia. But there are a number of issues that need to be addressed. One issue is that most of the studies conducted in recent year had taken a smaller sample size, which were not sufficient to generate significant results between schizophrenia patients and control groups. Another issue is that most of the studies did not take into account the influence of comorbidities such as diabetes and hypertension, age, gender of patients, antipsychotic medication dose and lifetime exposure, and smoking status etc. that could have affected the interpretations of the findings in these studies (as concluded by Silverstein et al., 2019). Another issue is that different studies were conducted using different OCT scanners, which, as a result, produced variable findings across the different studies that were conducted. Most of the studies were conducted using either a case-control or cross-sectional study approach and did not establish a longitudinal relation between retinal structural changes in relation to disease progression in schizophrenia patients. Also, considering the heterogeneity of this unique, yet complex disorder, another important question that still needs to be addressed is whether schizophrenia is a neurodevelopmental process that results in brain volume reduction well before the onset of the disease or if it is a neurodegenerative process that begins with the onset of the disease and progresses thereafter (Maynard et al., 2001). Further research into OCT studies might help answer this question as well in the near future.

Therefore, considering the established role of OCT as a reliable, easily accessible, relatively economic and pain-free neuroimaging technique in neurodegenerative disorders, there is a need to conduct larger studies in schizophrenia patients in order to assess retinal abnormalities and their relation with cognitive decline, as well as with disease progression, taking into account various parameters that affect the progression of the disease as well such as the influence of age, genetics, gender, and medical comorbidities just to name a few. In addition, there is a need to conduct longitudinal studies, ideally from the first episode of illness, in order to understand the progression of the changes in various retinal parameters in association with the progression of the disease.

In short, further research on the application of OCT and other neuroimaging techniques to correlate retinal structural alterations with schizophrenia may potentially help establish the role of retinal variables as biomarkers for the disease, and may open a gateway for better diagnostic investigations and help reduce disease-related disability in schizophrenia, and, as result, improve the prognosis of the disease.

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### Conflict of interest:

None To Declare.

### Method:-

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