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REVIEW ARTICLE

Could structural changes in the retinal layers be a new biomarker of mental disorders? A systematic review and thematic synthesis☆

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Abstract It has recently been suggested that alterations of the layers of the retina could be a biomarker of specific mental disorders since they originate in the same embryonic layer as the brain and both are interconnected through the optic nerve. The purpose of this article is to offer a systematic review of the literature and a thematic synthesis on the current state of the alterations of the retina layers identified by optical coherence tomography in patients with schizophrenia, bipolar disorder and major depression. For this purpose, we performed a bibliographic search, a systematic review of the studies and a thematic synthesis of the reported findings.

Patients with schizophrenia have more abnormal findings followed by patients with bipolar disorder, with very few findings in depression. The nerve fibre layer is the retinal layer with more abnormal findings both in schizophrenia and in bipolar disorder, while no study in major depression found alterations in it. Of the clinical parameters, the duration of the illness correlates significantly and inversely with the thickness of the different layers in all disorders.

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When interpreting these data, it is necessary to take into account the limitations and differences of the studies, especially the mean length of the disorders. Given that this was very different among the 3 disorders (more than doubled in the case of schizophrenia respect to major depression), the differences in the results found could be due more to the effect of the length of illness than to the disorder itself.

In summary, optical coherence tomography findings are promising, since they could provide biomarkers of neurodegeneration and/or neuroprogression of both schizophrenia and bipolar disorder.

PALABRAS CLAVE
Tomografía de coherencia óptica;
Retina;
Esquizofrenia;
Trastorno bipolar;
Depresión mayor

Los cambios estructurales de la retina, ¿nuevos biomarcadores de los trastornos mentales? Una revisión sistemática y síntesis temática de la literatura

Resumen Recientemente se ha planteado que las alteraciones de las capas de la retina podrían ser un biomarcador de determinados trastornos mentales, al derivar esta de la misma capa embrionaria que el cerebro y estar conectada con este a través del nervio óptico. El objeto del presente artículo es ofrecer una revisión sistemática de la literatura y una síntesis temática sobre el estado actual de las alteraciones de las capas de la retina identificadas mediante tomografía de coherencia óptica en los pacientes con esquizofrenia, trastorno bipolar y depresión mayor. Para ello se realizó una búsqueda sistemática de la literatura, la lectura crítica de los artículos seleccionados y la síntesis temática de los resultados.

Los pacientes con esquizofrenia son los que presentan más alteraciones, seguidos de los pacientes con trastorno bipolar, siendo muy escasos los hallazgos en la depresión. La capa de fibras nerviosas de la retina es la capa retiniana con más alteraciones en la esquizofrenia y en el trastorno bipolar, mientras que ningún estudio en depresión mayor encontró alteraciones en ella. De los parámetros clínicos, la duración de la enfermedad correlaciona significativa e inversamente con el grosor de las distintas capas en todos los trastornos.

A la hora de interpretar estos datos es necesario tener en cuenta las limitaciones y diferencias de los estudios, especialmente el tiempo medio de evolución de los trastornos. Dado que este era muy diferente entre los 3 trastornos (más del doble en el caso de la esquizofrenia respecto a la depresión mayor), las diferencias en los resultados encontrados podrían deberse más al efecto del tiempo de evolución que al trastorno en sí.

En conclusión, los hallazgos de la tomografía de coherencia óptica son esperanzadores, ya que podrían proporcionar biomarcadores de la neurodegeneración y/o neuroprogresión tanto de la esquizofrenia como del trastorno bipolar.

Introduction

Heading towards the end of the second decade of the 21st century, there are still no consistent data on the pathophysiology of severe mental disorders and their diagnosis continues leaning towards identifying the characteristic signs and symptoms through the clinical interview. However, the clinical presentation, especially in initial phases, can vary widely; dominant manifestations range from psychotic and/or affective signs and symptoms to a reduction in the level of functioning, passing through cognitive changes – such variability making it considerably more difficult to diagnose the illness precisely. The past 15 years have consequently seen significant efforts to identify objective, quantifiable markers that help to understand the pathophysiology of these disorders and to improve our diagnostic precision by incorporating biological markers.[1] Among the markers under study is brain imaging. However, despite its importance, neuroimaging has yet to demonstrate great usefulness in diagnosing these illnesses, besides being a relatively expensive method that is uncomfortable for patients.

Interest has recently been focused on the retina, given that it originates from the same embryonic layer as the brain and is connected to it through the optic nerve, like a window that makes it possible to observe the brain directly through its structure and/or function. Several authors[2–4] have suggested that changes in retinal structure might parallel or reflect changes in brain tissue, so retinal changes would be an easily-accessed marker of functional and/or structural brain integrity.

Optical coherence tomography (OCT) is a rapid, non-invasive imaging technique conducted without body contact and lacking known side effects. It provides precise, detailed in vivo visualisation of retinal architecture, especially in the

macula and fovea region. The axial slices that OCT provides make it possible to obtain an ''optical biopsy'' of the surface studied, showing the 10 layers conforming the retina in great detail. Considered the optical analogue of ultrasound imaging, the OCT technique features short pulses of infrared light aimed at the eye and a reference mirror. The difference between the pattern of spectral frequency returned by the eye (the profile of the original spectral frequency minus what is absorbed by the retinal structures) and the unaltered frequency returned by the reference mirror is used to reconstruct the retinal layer images in two or three dimensions. It represents the greatest technological advance in ophthalmology in recent years, becoming the diagnostic method par excellence for analysing and controlling the diseases that affect the retina and the optic nerve.

Currently, OCT is being used in researching neurodegenerative diseases such as multiple sclerosis, Parkinson's and Alzheimer's dementia. There is neurodegenerative parallelism between these illnesses and severe mental disorders, especially schizophrenia (SCH). Bearing this in mind, this technique has recently been incorporated into research on autism spectrum disorder, SCH, el bipolar disorder (BD) and major depression (MD), in order to establish whether its findings might be biomarkers of the neurodegeneration and/or neuroprogression characteristic of these disorders. The interest is also even greater because it is a non-invasive, rapidly applied technique that is more economical than the conventional neuroimaging techniques.

Several reviews have recently been published about retinal alterations identified using OCT in mental disorders.[4–7] However, these are limited to SCH, even though Adams and Nasrallah[6] also included a small summary of the findings in other mental disorders. That is the reason that our objective was to carry out a systematic review and qualitative thematic synthesis of alterations in the retina identified using OCT in individuals with SCH, BD and depression.

Methods

This article presents a systematic review and a thematic synthesis on the retina alterations identified using OCT in individuals with severe mental disorders, specifically SCH, BD and MD. First of all, a systematic literature search was carried out; next, the studies selected were read critically. Finally, a thematic synthesis of the retinal alterations described was created, and the areas for improvement based on the weaknesses of the studies analysed were identified.

Systematic literature search

A systematic search of the PubMed database, with no time limitation at all, was performed using the following search terms: (Optical Coherence Tomography [All Fields]) AND ((Schizophrenia [All Fields]) OR (Bipolar Disorder [All Fields]) OR (Major Depression [All Fields])). A total of 45 articles were obtained, of which 19 were selected (10 on SCH, 5 on depression, 3 on BD and 1 on psychosis). The same search was also repeated, but this time with the mental disorder search terms operating as MeSH Terms instead of All Fields, yielding a total of 22 articles. Of these, 19 had already been obtained in the previous search, while there were 3 new articles relevant for this review (1 for each disorder).

The relevance criteria established for selecting an article for analysis of results were that the article had to describe OCT results in patients with the chosen mental disorder and had to be written in Spanish or English. There were no restrictions as to sample size or study design. Based on these criteria, 8 more articles were eliminated, as follows: 1 on psychosis,[8] because it included 6 patients with 2 mental disorders (3 with SCH and 3 with BD) and did not provide the results separately for the two disorders; 5 on SCH, because they were reviews[4–7] or they included patients with schizoaffective disorder as well[2]; and 2 on depression,[9,10] because they consisted of a letter to the editor about the limitations of the article by Schönfeldt-Lecuona et al.[11] and the article authors' reply to the letter comments.

A search was also conducted in PsycINFO, as well as a manual search of the references of the articles identified, but no additional articles were found.

Critical reading of the articles

The articles on SCH were critically read by LGA, those on BD by LFT and those on depression by AVI. The first-named author (MPGP) also read all the articles independently. After that, a consensus was reached among the 4 authors on the weaknesses and strengths of the studies, and on the results obtained.

Thematic synthesis

To carry out the thematic synthesis, 2 main topics of interest were identified: alterations in the retina and choroid in each of the mental disorders, and the correlation between the retinal and choroidal alterations and the clinical variables for each disorder (time of evolution, psychometric and clinical severity, hospitalisations, treatment refractoriness, drug treatment). Each of the reviewers extracted the findings individually, organising them into these 2 topics, along with the limitations of the disorder studies. The first-named author unified and synthesised the findings on the 3 disorders and noted the pertinent assessments or functions.

Results

This systematic review and thematic synthesis on retinal alterations in individuals with severe mental disorder is based on a total of 14 articles: 6 on SCH, 4 on BD and 4 on depression.

Alterations in the retina in severe mental disorders (Table 1)

Schizophrenia

The few studies conducted using OCT in patients with SCH have shown mainly a global thinning of retinal thickness. This occurs especially at the expense of the photoreceptor layer, in the fovea and the nasal and temporal parafoveal areas,[12] but also of the global thickness of the retinal nerve fibre layer (RNFL)[3,13–15] and in the superior and inferior

Table 1 Differences between patients and healthy control subjects in the optical coherence tomography parameters.

First author, year and country	Type of study	Study subjects	Technique	Study parameters	Results
Schizophrenia					
Samani et al.,[12] 2018, United Kingdom	Cases and controls	35 patients with SCH, mean age 40.6 years, mean time of disease progression 16.3 years 50 healthy control subjects	SD-OCT	Total thickness of the retina and of the different layers	Total retinal thickness less ($p < .05$) in the fovea and in the temporal and nasal parafoveal areas in patients than in controls Thickness of the PISL, ONL and photoreceptor layers less ($p < .05$) in the fovea and the temporal and nasal parafoveal areas in patients than in controls RNFL and IPL thickness less ($p < .05$) in the nasal parafoveal area in patients than in controls GCL thickness less ($p < .05$) in the temporal parafoveal area in patients than in controls
Silverstein et al.,[16] 2018, USA	Cases and controls matched at group level, for age and sex	32 patients with SCH: 21 without D/HBP and 11 with D/HBP Mean ages: 40.5 years for all patients and 35.1 and 50.9 years for each subgroup, respectively 32 healthy controls: 21 without D/HBP and 11 with D/HBP	SD-OCT	Global RNFL thickness and thickness of 4 quadrants, and RNFL symmetry GCL-CPI thickness Macular volume and thickness of 4 quadrants Optic nerve head: optic cup volume and cup/disc ratio	No differences in RNFL symmetry and thickness between either patients-controls or between the 4 groups No differences in GCL-CPI thickness between patients and controls Patients with D/HBP thinner ($p < .05$) than controls without D/HBP Macular thickness in left nasal outer quadrant less ($p < .05$) in patients than in controls Patients with D/HBP thinner ($p < .05$) in all quadrants except the lower in both eyes compared with patients without D/HBP and controls without D/HBP Optic cup volume greater ($p < .05$) in right eye in patients than in controls Cup/disc ratio greater ($p < .05$) in both eyes in patients than in controls Patients with and without D/HBP have greater cup/disc ratio ($p < .05$) than controls with and without D/HBP Patients and controls with D/HBP have thinning ($p < .05$) of the majority of the retinal structures, especially in the left eye, compared with patients and controls without D/HBP

Table 1 (*Continued*)

First author, year and country	Type of study	Study subjects	Technique	Study parameters	Results
Celik et al.,[15] 2016, Turkey	Cases and controls	40 patients with TR-SCH and 41 patients with SCH-rT, mean ages 35.7 and 35.4 years, respectively, mean time of disease progression 14.5 and 12.0 years, respectively 41 healthy controls	SD-OCT	Global RNFL thickness and thickness of 6 quadrants GCL and IPL volume Choroidal thickness	Global RNFL thickness in right eye and in the upper and lower quadrants less ($p < .05$) in patients than in controls GCL and IPL volume in right eye less ($p < .05$) in patients than in controls GCL and IPL volume in right eye less ($p < .05$) in patients with TR-SCH vs with SCH-rT Choroidal thickness in right eye less ($p < .05$) in patients with TR-SCH vs with SCH-rT
Ascaso et al.,[14] 2015, Spain	Age- and sex-matched cases and controls	30 patients with SCH: 10 RE (recent episode) (in the last month) and 20 N-RE (no recent episode) (stable and no episodes in the last 6 months) Mean ages: 45.1 for all patients and 41.5 and 46.8 years for each subgroup, respectively Mean time of disease progression: 16 years for all patients and 17.6 and 13.7 years for each subgroup 30 healthy controls	TD-OCT	Global RNFL thickness and thickness of 4 quadrants Macular thickness (inner and outer rings and fovea) and volume	Thickness of global RNFL in right eye and in upper quadrant, in left eye in lower less ($p < .05$) in patients than in controls In N-RE patients, global RNFL thickness in right eye and in upper and nasal quadrants less ($p < .05$) than in RE patients and controls Inner ring thickness, fovea and macular volume in left eye less ($p < .05$) in patients than in controls In N-RE patients, inner ring thickness in right eye and macular volume in left eye less ($p < .05$) than in RE patients and controls In N-RE and RE patients, inner ring thickness in left eye less ($p < .05$) than in controls
Ascaso et al.,[13] 2010, Spain	Age-matched cases and controls	10 patients with SCH, mean age 39.2 years 10 healthy controls	TD-OCT	Global RNFL thickness and thickness of 4 quadrants Macular thickness and volume Optic nerve head (cup/disc ratio and horizontal and vertical ratios)	Global RNFL thickness and thickness in nasal quadrant nasal less ($p < .05$) in patients than in controls

Table 1 (*Continued*)

First author, year and country	Type of study	Study subjects	Technique	Study parameters	Results
Lee et al.,[3] 2013, Malaysia	Cases and controls matched for age, sex and race	30 patients with SCH, mean age 37.2 years 5 acute (duration of disorder $\leq$2 years) 13 chronic (>2–10 years) 12 long-term chronic patients (>10 years) 30 healthy controls	SD-OCT	Global RNFL thickness and thickness of 4 quadrants Global macular thickness, in the inner and outer rings and in central area, and macular volume	Global RNFL thickness and in quadrants superior, inferior and temporal less ($p < .05$) in patients than in controls Global RNFL thickness less ($p < .05$) in chronic and long-term chronic patients than in controls and acute Global macular thickness, in the inner and outer rings and in central area, macular volume less ($p < .05$) in patients than in controls Global macular thickness less ($p > .05$) in chronic and long-term chronic patients than in controls, and in long-term chronic than acute patients Macular volume less ($p < .05$) in chronic and long-term chronic patients than in controls, and in long-term chronic than acute patients
Bipolar disorder					
García-Martín et al.,[19] 2018, Spain	Cases and controls	30 patients with BD, mean age 49.7 years and mean time of disease progression 16.5 years 80 healthy controls	SD-OCT	Total thickness of the retina and of the different layers Volume of the retina, GCL, IPL and INL	Total retinal thickness less ($p < .005$) in upper, nasal and temporal inner ring and in upper outer ring in patients than in controls Global peripapillary RNFL, upper temporal, temporal and lower temporal thickness ($p < .005$) in patients vs controls GCL thickness of upper, nasal, lower and temporal inner ring less ($p < .05$) in patients than in controls IPL thickness in nasal, lower and temporal inner ring less ($p < .05$) in patients than in controls Minimum central IPL thickness more reduced ($p < .05$) in patients than in controls INL thickness in the upper and temporal inner ring, and in the upper, nasal, lower and temporal outer ring greater ($p < .05$) in patients than in controls Global GCL volume less ($p < .05$) in patients than in controls Global INL volume higher ($p < .05$) in patients than in controls

Table 1 (*Continued*)

First author, year and country	Type of study	Study subjects	Technique	Study parameters	Results
Khalil et al.,[18] 2017, Egypt	Age- and sex-matched cases and controls	40 hospitalised patients with BD-I without psychotic symptoms, mean age 30.9 years and mean time of disease progression 7 years 40 healthy controls	SD-OCT	Global thickness of RNFL and of the 4 quadrants Global, upper and lower GCL volume	Global RNFL thickness and thickness in all the quadrants except for the nasal less ($p < .05$) in patients than in controls Global GCL volume in both eyes and upper and lower only in the left eye less ($p < .05$) in patients than in controls
Kalenderoglu et al.,[20] 2016, Turkey	Cases and controls	43 patients with BD-I in euthymia for 6 months, mean age 35.5 years and mean time of disease progression 6.8 years 43 healthy controls	SD-OCT	Global RNFL thickness and thickness of 6 quadrants, and of the choroid GCL volume	Global RNFL thickness less ($p < .05$) in patients than in controls Global RNFL thickness less ($p < .05$) in patients in treatment with valproate than in treatment with lithium or without either of these 2 drugs GCL volume less ($p < .05$) in patients than in controls
Mehraban et al.,[17] 2016, Iran	Age-matched cases and controls	30 patients with BD, mean age 33.8 years and mean time of disease progression 10.6 years 30 healthy controls	3D-OCT	Global RNFL thickness and of the 4 quadrants	Global RNFL thickness and thickness in all quadrants (except for the temporal) less ($p < .05$) in patients than in controls
Major depression					
Schöenfeldt-Lecuona et al.,[11] 2018, Germany	Age-matched cases and controls	28 patients with MD, mean age 46.9 years and mean time of disease progression 5.3 years 20 healthy controls	SD-OCT	Total volume and thickness of the retina Volume and thickness of 5 retinal layers	No significant differences in any parameters between patients and controls Patients showed significant difference in total retinal volume between the 2 eyes
Sönmez et al.,[22] 2017, Turkey	Age- and sex-matched cases and controls	30 patients with MD, mean age 34.5 years and mean time of disease progression 5.7 years 30 healthy controls	OCT	Global RNFL thickness and thickness of 6 quadrants	No significant differences in any parameters between patients and controls

Table 1 (*Continued*)

First author, year and country	Type of study	Study subjects	Technique	Study parameters	Results
Kalenderoglu et al.,[23] 2016, Turkey	Cases and controls	50 patients with FE-MD and 50 patients with RDD, mean ages 39.1 and 40.8 years, respectively 50 healthy controls	SD-OCT	Thickness of the RNFL GCL and IPL volume Choroidal thickness	Volume GCL and IPL less ($p < .05$) in patients than in controls GCL and IPL volume less ($p < .05$) in patients with RDD than in those with FE-MD Choroid thicker ($p < .05$) in patients than in controls Choroid thicker ($p < .05$) in patients with RDD than in those with FE-MD
Yildiz et al.,[21] 2016, Turkey	Cases and controls	58 patients with MD, mean age 44.6 years and mean time of disease progression 6.5 years 57 healthy controls	HD-OCT	Global RNFL thickness and thickness of 4 quadrants GC-IPL thickness Macular thickness	No significant differences in any parameters between patients and controls

BD: bipolar disorder; D: diabetes; FE-MD: first episode of major depression; GCL: ganglion cell layer; GC-IPL: ganglion cell layer and inner plexiform layer; HBP: high blood pressure; HD-OCT: high-domain optical coherence tomography; INL: inner nuclear layer; IPL: inner plexiform layer; MD: major depression; OCT: optical coherence tomography; ONL: outer nuclear layer; PISL: photoreceptor inner segment layer; RDD: recurrent depressive disorder; RNFL: retinal nerve fibre layer; SCH: schizophrenia; SCH-rT: schizophrenia with response to treatment; SD-OCT: spectral-domain optical coherence tomography; TD-OCT: time-domain optical coherence tomography; TR-SCH: treatment-resistant schizophrenia.

quadrants,[3,14] and loss of volume in the ganglion cell layer (GCL)[15] and in the inner plexiform layer (IPL)[15] compared with healthy controls. In addition, patients that had comorbidities with systemic diseases such as diabetes or high blood pressure (HBP) showed thinner GCL and IPL areas than the controls that did not have diabetes or HBP, and a thinner macula than the patients and controls without diabetes or HBP.[6]

Likewise, differences between patients and controls have been described at the level of the macula[3,14,16] and optic disc.[16] Comparing patient macula with those of healthy controls, patients presented less macular thickness[3,16] and volume,[3,14,16] as well as thinning in the fovea and the outer[3] and inner rings.[3,14] As for optic disc alterations, patients presented greater cup volume and a greater cup/disc ratio than healthy controls.[16]

Bipolar disorder

The 4 studies published on BD showed a considerable reduction in RNFL thickness in the patients with BD compared with the healthy controls, the location of this alteration differing. Mehraban et al.[17] described a notable reduction in the inferior, superior and nasal quadrants; Khalil et al.,[18] in the inferior, superior, temporal and global quadrants; García-Martín et al.,[19] in the upper temporal, temporal, lower temporal and global quadrants; and Kalenderoglu et al.,[20] in only the global. In addition, Kalenderoglu et al.,[20] Khalil et al.[18] and García-Martín et al.[19] showed that GCL volume was less in the patients with BD than this volume in the control subjects. The last-mentioned authors also found reduced inner ring thickness in the 4 quadrants of the GCL compared with the healthy controls. As for IPL, García-Martín et al.[19] described a reduction in the inner ring of the inferior, nasal and temporal quadrants, along with a reduction in the minimum central thickness in comparison with the controls. Lastly, these same authors found a global increase in the volume of the inner nuclear layer, specifically in inner ring thickness in the superior and inferior quadrants, and in the outer ring in the 4 quadrants.

Major depression

In the case of MD, 3 of the 4 studies published did not show significant differences between the patients and the healthy controls in any of the OCT parameters studied.[11,21,22] Only Kalenderoglu et al.[23] found less GCL and IPL volume in patients with MD than in healthy controls, and in patients with multiple episodes than in those with a single episode.

Schöenfeldt-Lecuona et al.[11] found the total volume of the left eye retina was significantly greater than that of the right eye (8.72 vs 8.69 mm^3, $p = .03$) in patients with MD.

Choroidal alterations in severe mental disorders (Table 1)

The studies reviewed described alterations in choroidal thickness solely in the patients with MD. Specifically, Kalenderoglu et al.[23] found that the patients with MD showed a greater choroidal thickness than the healthy controls did; the same occurred for the patients with multiple episodes compared with the patients that had had a single episode.

Correlation between ocular alterations and clinical dimensions (Table 2)

Schizophrenia

With respect to the impact of time of evolution on ocular alterations, Lee et al.[3] demonstrated that global RNFL was thinner in patients with more than 2 years of disorder evolution than in patients with less than 2 years of evolution and in controls. In addition, in patients without a recent episode (defined as >6 months since the last episode), they found significant reductions in global RNFL thickness and in the thickness of the superior, inferior and nasal quadrants compared with the controls; the thickness of the inner ring of the macula and macular volume were reduced as well.[14] Likewise, they observed a thinning in the inner ring of the macula[3,14] and a loss of macular volume[3,14] in advanced stages of the disease compared with the control subjects.[16]

The relationship between the different psychopathological dimensions of SCH and changes in retinal architecture have also been investigated. Samani et al.[12] found a significant moderate inverse correlation between the severity of negative SCH symptoms and the thickness of the photoreceptor ($r = -.54$) and outer nuclear layers ($r = -.47$) in the fovea. Cognitive symptoms were shown to be related with increased cup volume in both eyes (left, $r = .48$; right, $r = .45$) and increased cup/optic disc ration in the right eye ($r = .41$).[16] These authors also found a significant direct correlation between antipsychotic drug dose (chlorpromazine equivalents) and cup volume in both eyes (left, $r = .41$; right, $r = .38$).

Lastly, patients with treatment-refractory SCH showed a greater reduction in GCL and IPL volume than patients with an adequate response to treatment.[15]

Bipolar disorder

The time of BD evolution correlated significantly and inversely with global RNFL thickness ($r = -.250$,[20] non-proportional value of r[17]) and GCL thickness ($r = -.466$).[20] Disorder evolution time directly correlated with the minimum central thickness of the GCL ($r = .70$)[19] and the upper outer quadrant thickness of the outer plexiform layer ($r = .49$).[19] In addition, there was significant direct correlation between the number of manic episodes and RNFL thickness in the inferior quadrant of the right eye ($r = .335$).[18]

As for clinical severity, Khalenderoglu et al.[20] demonstrated significant inverse correlations between the scores on the Young Mania Rating Scale and the Clinical Global Impression Scale (CGI) and the number of hospitalisations with global RNFL thickness ($r = -.265$, $-.280$ and $-.232$, respectively) and with GCL thickness ($r = -.407$, $-.456$ and $-.431$, respectively).

Major depression

A significant inverse correlation of time of disorder evolution has been described with GCL and IPL layer volume ($r = -.247$ and $-.252$, respectively) and with choroidal thickness ($r = -.329$).[23] Inverse correlations between the duration of the last depressive episode and the thickness of the RNFL

Table 2 Correlations between the optical coherence tomography parameters and the clinical characteristics of the illness.

First author, year and country	Type of study	Study subjects	Results
Schizophrenia			
Samani et al.,[12] 2018, United Kingdom	Cases and controls	35 patients with SCH	Significant inverse correlations ($p < .05$) between: Duration of disorder and thickness of the PISL, ONL and temporal parafoveal photoreceptor layers Negative PANSS score and thickness of total retinal, ONL and foveal photoreceptor layers and nasal parafoveal area PANSS score-general severity and ONL nasal parafoveal thickness
Silverstein et al.,[16] 2018, USA	Cases and controls matched at group level, for age and sex	32 patients with SCH: 21 without D/HBP and 11 with D/HBP	Direct significant correlations ($p < .05$) between: PANSS score-cognitive and cup/disc ratio in right eye, and cup volume in both eyes Chlorpromazine equivalents and cup volume in both eyes
Celik et al.,[15] 2016, Turkey	Cases and controls	40 patients with TR-SCH 41 patients with SCH-rT	Significant inverse correlations ($p < .05$) between: Duration of disorder and choroidal thickness and GCL volume in right eye PANSS score and GCL and IPL volume in right eye CGI score and GCL and IPL volume in right eye Number of hospitalisations and choroidal thickness and GCL and IPL volumes in right eye
Ascaso et al.,[14] 2015, Spain	Age- and sex-matched cases and controls	30 patients with SCH: 10 RE and 20 N-RE	No significant correlations between duration of disorder and OCT parameters, after controlling for age
Lee et al.,[3] 2013, Malaysia	Cases and controls matched for age, sex and race	30 patients with SCH: 5 acute, 13 chronic and 12 long-term chronic patients	Significant inverse correlations ($p < .05$) between: Duration of disorder and global RNFL thickness and thickness in upper quadrant, and global thickness and thickness of inner and outer rings and macular volume
Bipolar disorder			
García-Martín et al.,[19] 2018, Spain	Cases and controls	30 patients with BD	Direct significant correlation ($p < .05$) between: Duration of disorder and thickness of outer upper quadrant of the OPL and minimum central GCL thickness
Khalil et al.,[18] 2017, Egypt	Age- and sex-matched cases and controls	40 patients hospitalised with BD-I without psychotic symptoms	Direct significant correlation ($p < .05$) between: Number of manic episodes and RNFL thickness in lower quadrant in right eye
Kalenderoglu et al.,[20] 2016, Turkey	Cases and controls	43 patients with BD-I in euthymia	Significant inverse correlations ($p < .05$) between: Duration of disorder and global RNFL and GCL thickness YMRS score and global RNFL and GCL thickness CGI score and global RNFL thickness and GCL thickness Number of hospitalisations and global RNFL thickness and GCL thickness

Table 2 (*Continued*)

First author, year and country	Type of study	Study subjects	Results
Mehraban et al.,[17] 2016, Iran	Age-matched cases and controls	30 patients with BD	Significant correlation ($p < .05$) between: Duration of disorder and global RNFL thickness
Major depression			
Schöenfeldt-Lecuona,[11] 2018, Germany	Age-matched cases and controls	28 patients with MD	No significant correlations between duration of disorder/BDI and MADRS depression scale scores/number of hospitalisations and the OCT parameters
Kalenderoglu et al.,[23] 2016, Turkey	Cases and controls	50 patients with PE-MD 50 patients with RDD	Significant inverse correlations ($p < .05$) between: Duration of disorder and choroidal thickness, and GCL and IPL volume HDRS score and choroidal thickness, and GCL and IPL volume CGI score and global RNFL thickness, and GCL and IPL volume
Yildiz et al.,[21] 2016, Turkey	Cases and controls	58 patients with MD	Significant inverse correlations ($p < .05$) between: Duration of last depressive episode and RNFL thickness in nasal quadrant and GC-IPL Significant direct correlation ($p < .05$) between: QIDS score and global RNFL thickness

BD: bipolar disorder; BDI: Beck Depression Inventory; CGI: Clinical Global Impression Scale; D: diabetes; FE-MD: first episode of major depression; GC-IPL: ganglion cell layer and inner plexiform layer; GCL: ganglion cell layer; HBP: high blood pressure; HD-OCT: high-domain optical coherence tomography; HDRS: Hamilton Depression Rating Scale; IPL: inner plexiform layer; MADRS: Montgomery-Asberg Depression Rating Scale; MD: major depression; N-RE: no recent episode (stable and no episodes in the last 6 months); OCT: optical coherence tomography; ONL: outer nuclear layer; OPL: outer plexiform layer; PANSS: Positive and Negative Syndrome Scale; PISL: photoreceptor inner segment layer; QIDS: Quick Inventory of Depressive Symptomatology; RDD: recurrent depressive disorder; RE: recent episode (in the last month); RNFL: retinal nerve fibre layer; SCH: schizophrenia; SCH-rT: schizophrenia with response to treatment; SD-OCT: spectral-domain optical coherence tomography; TD-OCT: time-domain optical coherence tomography; TR-SCH: treatment-resistant schizophrenia; YMRS: Young Mania Rating Scale.

in the nasal quadrant ($r = -.31$) and of the ganglion cell and inner plexiform layers (GC-IPL) ($r = -.32$) have also been described.[21]

Likewise, there were significant correlations between the clinical severity of the depression and the OCT parameters. Scores on the Hamilton Depression Rating Scale correlated inversely and significantly with GCL and IPL volume ($r = -.200$ and $-.221$, respectively) and with choroidal thickness ($r = -.180$).[23] Scores on the Quick Inventory of Depressive Symptomatology-Self Report directly correlated with total RNFL thickness ($r = .28$). Although CGI scores correlated inversely and significantly with GCL and IPL volume ($r = -.248$ and $-.268$, respectively), they correlated with global RNFL thickness ($r = -.162$) instead of with that of the choroid.[23]

Lastly, taking antipsychotic drugs was significantly associated with less GCL and IPL volume.[23]

Discussion

As has been indicated in the result section, there are few studies using OCT in mental disorders such as SCH, BD and MD. This is in contrast with what happens in dementia or in neurological diseases such as Parkinson's. In addition, the results obtained are sometimes divergent, and even contradictory.

Among all the retinal parameters evaluated, RNFL thickness is undoubtedly the one that has provided the most significant findings in the 3 mental disorders reviewed. With a single exception,[16] all the studies conducted on patients with SCH or BD show significant thinning compared with the healthy controls, while none of the 4 studies on MD find significant alterations. These differences among the 3 disorders might indicate that MD, in contrast to SCH and BD, is not associated with a magnocellular pathway alteration, as Sönmez et al.[22] noted. However, based on the hypothesis of neurodegeneration and the capability of OCT to identify it, the differences might be related to the time of evolution of the disorder more than to the disorder itself: the time of evolution for the patients with MD (from 5.5 to 6.5 years in the 4 studies) was much shorter than the time of evolution for the patients with BD (in 3 studies, it was between 7 and 10 years and was only greater than 10 years – specifically 16.5 years – in 1 study) and, above all, shorter than that of the patients with SCH (between 12 and 16 years). In the patients with SCH, the findings of Lee et al.[3] and Ascaso et al.[14] were congruent with this, which would reinforce the

hypothesis that the retinal alterations were the expression of the progressive neurodegeneration of the disorder. These researchers showed that RNFL thinning was greater in long-term chronic (>10 years of evolution) and chronic (>2–10 years) patients than in acute patients (≤2 years) and healthy controls.[3] They also showed that such thinning was more in patients without a recent episode (no episodes in the last 6 months) than in patients with a recent episode (the last month) and healthy control subjects.[14]

Other retinal layers that have provided significant results are the GCL and the IPL. Significant differences are obtained in comparison to results for the controls in the 3 disorders studied, even though the consistency of the findings is low. GCL thickness/volume is significantly less than those of the controls in 2 of the 6 studies on SCH,[12,15] in 3 of the 4 studies on BD[18–20] and in 1 of the 4 studies on MD.[23] In addition, the IPL also presented less volume in SCH,[15] in BD[19] and in MD.[23] The fact that the GCL-IPL alterations are more pronounced than those of the RNFL in BD[20] and that they are the only retinal alterations described for MD[23] would support the hypothesis of González-López et al.[24] that the GCL-IPL would be more sensitive than the RNFL in the detection of alterations in retinal structure, bearing in mind the findings obtained in patients with multiple sclerosis. In addition, the shorter time of disease evolution in the case of MD and BD compared with that of SCH would also support the hypothesis of neuroprogression: patients with shorter time of evolution would only show alterations in the GCL-IPL, which would progress until reaching the RNFL. Along this line, Kalenderoglu et al.[23] indicated that there was less volume in both layers in the patients with multiple episodes of depression than in the patients with a single episode. However, even though Silverstein et al.[16] found no significant differences between patients and controls, they did find them between the subgroup of patients with diabetes or hypertension compared with the subgroup of controls that did not have these conditions. These authors, in contrast to what occurred in most of the studies conducted, included a subgroup of patients and controls with diabetes or hypertension without identifiable retinal involvement in order to determine whether the alterations described in the studies were truly due to the mental disorder or if they might be due to systemic diseases with a known ocular impact that are frequently comorbid with SCH. Their results demonstrated that the retinal alterations were due more to the presence of diabetes or hypertension than to SCH (although it is necessary to point out that the group of patients with diabetes and hypertension were significantly older than the patients and the controls without diabetes or hypertension). As for the impact of drug treatment on these 2 layers (GCL and IPL), less volume of both was found in the patients with treatment-resistant SCH than in those responding to treatment,[15] and in the patients with MD under antipsychotic drug treatment than in those not taking such drugs.[23] These results show that being refractory to drugs is related to greater neurodegeneration in both disorders.

The impact of psychopharmaceutical drugs on the retinal alterations found is a controversial subject that requires additional, in-depth studies. It has been proposed that the effect might be explained by the dopaminergic block of antipsychotics[16] or by their serotoninergic effect and their impact on intraocular pressure.[25] However, it should be pointed out that valproate (which lacks these mechanisms of action) has also been associated with a thinner RNFL, while lithium has not.[20]

Alterations in choroidal thickness have seldom been described and the data have been controversial. While no differences were found between the patients and controls in the study on SCH,[15] in MD Kalederoglu et al.[23] described a thickening of the choroidal layer in the patients compared with the controls, a fact that they attributed to the inflammatory state characterising the active disease. The results of Celik et al.[15] were to a certain degree contrary to this hypothesis: in spite of the fact that treatment-resistant SCH has been associated with low-grade chronic peripheral inflammation,[26] these authors found thinning of the choroid in the patients with treatment-resistant SCH compared with patients responding to treatment.

The relationship between the ocular alterations and the clinical parameters varies widely and has not been regularly replicated in these studies, except for the time of disease evolution. In all the disorders, and in most of the studies on each disorder, a direct relationship has been described between the time of evolution and the retinal alterations described, which supports the hypothesis of neuroprogression in these mental disorders. In the case of SCH, correlations have also been described, as expected, between the scores on the Positive and Negative Syndrome Scale-negative and general,[12] the Positive and Negative Syndrome Scale-cognitive,[16] the Positive and Negative Syndrome Scale and the CGI-G[15] with different retinal alterations. In addition, the chlorpromazine equivalents[16] and the number of hospitalisations correlated as expected with the optic cup volume in both eyes, and choroidal thickness and IPL and GCL volume in the right eye, respectively. In the case of BD, only 1 study out of the 3[20] found direct correlations between psychopathological severity (scores on the Young Mania Rating Scale and on the CGI) and retinal alterations (thickness of the RNFL and the GCL). However, considering other indexes of disorder severity, the number of hospitalisations[20] has been associated with RNFL and GCL thickness, and the number of manic episodes,[18] with RNFL thickness. Nonetheless, it should be pointed out that, for the number of manic episodes, the correlation was not in the expected sense (that is, the greater the number of manic episodes, the thicker the RNFL), and the authors[18] did not offer a plausible explanation for this finding. Lastly, the results described are contradictory in the case of MD: while greater self-evaluated clinical severity (as indicated by scores on the Hamilton Depression Rating Scale and the CGI) has been associated with retinal structure thinning,[23] greater self-evaluated clinical severity (Quick Inventory of Depressive Symptomatology scores) has also been associated with RNFL thickening.[21]

In evaluating the findings described here, the important methodological limitations that the studies reviewed present have to be considered. These limitations involve, in the first place, the study sample: study size and patient selection, the process of matching with control subjects, and the inclusion and exclusion criteria are questionable and vary from one study to another. In the majority of the studies, sample size ranges from 30 to 50 subjects per group, but the groups are sometimes subdivided and analysed based on some specific criterion (for example, with/without

diabetes/hypertension, acute vs chronic vs long-term chronic patients, etc.); this reduces the sample size and statistical power even more. A very important parameter is the time of disease evolution, as has been seen upon comparing the results of the 3 disorders reviewed: it can be essential when interpreting the results. Disorder stage and evolution (acute vs chronic and single episodes vs multiple episodes) present similar importance. In addition, given the complex nature of BD, patient heterogeneity is crucial to control. Matching between patients and controls is not always present in the studies, nor is it always at an individual level. In the most recent studies, the criteria for subject inclusion and exclusion are stricter and more numerous than in the initial studies; and the fact that patients with somatic comorbidities without identifiable clinical ophthalmological effects were included[16] makes some of the results for SCH to date questionable. As for technique, when the studies were performed once again generates differences: the most recent studies use spectral domain equipment, so the capability of detecting anomalies is better than that of the previous studies that used temporal domain OCT. The fact that the discrepancies in the findings might be partially caused by the non-homologation of devices used should also be considered. Finally, the statistical analysis is problematic. Most of the studies, especially the oldest, did not control for possibly confounding variables such as age, time of evolution of the disease and other factors that can interfere with the results. Although the limitations that we have indicated are numerous, they are ones that are frequently common in pioneering studies using a novel technique or intervention, and are overcome bit by bit as knowledge accumulates.

Among the limitations of this study, the fact that the sole source of information was PubMed should be mentioned. Nonetheless, this was because the PsycINFO search did not add any new studies. Although the lack of statistical analyses could be considered another limitation, the studies for each disorder are very limited and are on very diverse optical zones; these facts rule out conducting a metaanalysis of the results.

In short, the results of the OCT studies on patients with severe mental disorders back the existence of a gradient of neurodegeneration in these disorders, with the retinal alterations being more numerous and more consistent in SCH and in BD. The fact that such findings have not been found for MD might be due to either the shorter time of disease progression in the patients studied (which would lend weight to the hypothesis of neuroprogression), or to a lack of degeneration or an incapacity of OCT to identify it in this disorder. The fact that one of the studies has identified alterations in the GCL and IPL (layers that have shown to have a greater sensitivity in diseases such as multiple sclerosis) would also support neuroprogression in these 3 mental disorders. Lastly, except for time of disease progression, the retinal findings do not seem to mark differential clinical or psychopathological aspects in any of these disorders.

Bearing in mind everything that has been indicated above, the OCT findings are promising, because they could provide biomarkers of neurodegeneration and/or neuroprogression in both SCH and BD.

Conflict of interests

The authors have no conflicts of interest to declare.

References

1. Meana J, Mollinedo-Gajate I. Biomarcadores en Psiquiatría: entre el mito y la realidad clínica. Rev Psiquiatr Salud Ment. 2017;10:183–4.
2. Chu EM, Kolappan M, Barnes TR, Joyce EM, Ron MA. A window into the brain: an in vivo study of the retina in schizophrenia using optical coherence tomography. Psychiatr Res. 2012;203:89–94.
3. Lee WW, Tajunisah I, Sharmilla K, Peyman M, Subrayan V. Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: evidence from optical coherence tomography. Invest Ophthalmol Vis Sci. 2013;54:7785–92.
4. Schönfeldt-Lecuona C, Kregel T, Schmidt A, Pinkhardt EH, Lauda F, Kassubek J, et al. From imaging the brain to imaging the retina: optical coherence tomography (OCT) in schizophrenia. Schizophr Bull. 2016;42:9–14.
5. Silverstein SM, Rosen R. Schizophrenia and the eye. Schizophr Res Cogn. 2015;2:46–55.
6. Adams SA, Nasrallah HA. Multiple retinal anomalies in schizophrenia. Schizophr Res. 2018;195:3–12.
7. Hosak L, Sery O, Sadykov E, Studnicka J. Retinal abnormatilites as a diagnostic or prognostic marker of schizophrenia. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2018;162:159–64.
8. Joe P, Ahmad M, Riley G, Weissman J, Smith RT, Malaspina D. A pilot study assessing retinal pathology in psychosis using optical coherence tomography: choroidal and macular thickness. Psychiatry Res. 2018;263:158–61.
9. Ferro Desideri L, Barra F, Skhiri MI, Ferrero S. Methodological concerns on retinal thickness evaluation by spectral domain optical coherence tomography in patients with major depressive disorder. J Affect Disord. 2018;238:226–7.
10. Schönfeldt-Lecuona C, Schmidt A, Kregel T, Kassubek J, Dreyhaupt J, Freudenmann RW, et al. Response letter: retinal changes in patients with major depressive disorder – a controlled optical coherence tomography study. J Affect Disord. 2018;239:123.
11. Schönfeldt-Lecuona C, Schmidt A, Kregel T, Kassubek J, Dreyhaupt J, Freudenmann RW, et al. Retinal changes in patients with major depressive disorder – a controlled optical coherence tomography study. J Affect Disord. 2018;227:665–71.
12. Samani NN, Proudlock FA, Siran V, Suraweera C, Hutchinson C, Nelson CP, et al. Retinal layer abnormalities as biomarkers of schizophrenia. Schizophr Bull. 2018;44:876–85.
13. Ascaso FJ, Cabezón L, Quintanilla MA, Gutiérrez Galve L, López-Antón R, Cristóbal JA, et al. Retinal nerve fiber layer thickness measured by optical coherence tomography in patients with schizophrenia: a short report. Eur J Psychiatry. 2010;24:227–35.
14. Ascaso FJ, Rodríguez-Jiménez R, Cabezón L, López-Antón R, Santabárbara J, de la Cámara C, et al. Retinal nerve fiber layer and macular thickness in patients with schizophrenia: influence of recent illness episodes. Psychiatry Res. 2015;229:230–6.
15. Celik M, Kalenderoglu A, Karadag AS, Egilmez OB, Han-Almis B, Simsek A. 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. 2016;32:9–15.

16. Silverstein SM, Paterno D, Cherneski L, Green S. Optical coherence tomography indices of structural retinal pathology in schizophrenia. Psychol Med. 2018;48:2023–33.
17. Mehraban A, Samini SD, Entezari M, Seifi MH, Nazari M, Yaseri M. Peripapillary retinal nerve fiber layer thickness in bipolar disorder. Graefes Arch Clin Exp Ophthalmol. 2016;254:365–71.
18. Khalil MA, Saleh AA, Gohar SM, Khalil DH, Said M. Optical coherence tomography findings in patients with bipolar disorder. J Affect Disord. 2017;218:115–22.
19. García-Martín E, Gavin A, García-Campayo J, Vilades E, Orduna E, Polo V, et al. Visual function and retinal changes in patients with bipolar disorder. Retina. 2018, http://dx.doi.org/10.1097/IAE.0000000000002252.
20. Kalenderoglu A, Sevgi-Karadag A, Celik M, Egilmez OB, Han-Almis B, Ozen ME. Can the retinal ganglion cell layer (GCL) volume be a new marker to detect neurodegeneration in bipolar disorder? Compr Psychiatry. 2016;67:66–72.
21. Yildiz M, Sait A, Batmaz S, Demir S, Songur E, Ortak H, et al. Duration of the depressive episode is correlated with ganglion cell inner plexiform layer and nasal retinal fiber layer thicknesses: optical coherence tomography findings in major depression. Psychiatry Res Neuroimag. 2016;251:60–6.
22. Sönmez I, Köşger F, Aykan Ü. Retinal nerve fiber layer thickness measurement by spectral-domain optical coherence tomography in patients with major depressive disorder. Noro Psikiyatr Ars. 2017;54:62–6.
23. Kalenderoglu A, Çelik M, Sevgi-Karadag A, Egilmez OB. Optic coherence tomography shows inflammation and degeneration in major depressive disorder patients correlated with disease severity. J Affect Disord. 2016;204:159–65.
24. González-López JJ, Rebolleda G, Leal M, Oblanca N, Muñoz-Negrete FJ, Costa-Frossard L, et al. Comparative diagnostic accuracy of ganglion cell-inner plexiform and retinal nerve fiber layer thickness measures by Cirrus and Spectralis optical coherence tomography in relapsing-remitting multiple sclerosis. Biomed Res Int. 2014;2014:128517.
25. Souza VB, Moura Filho FJ, Souza FG, Pereira Filho SA, Coelho SS, Furtado FA, et al. Intraocular pressure in schizophrenic patients treated with psychiatric medications. Arq Bras Oftalmol. 2008;71:660–4.
26. Fond G, Lançon C, Auquier P, Boyer L. C-reactive protein as a peripheral biomarker in schizophrenia. An updated systematic review. Front Psychiatry. 2018;9:392.