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ARTICLE

Can retinal nerve fiber layer (RNFL) thickness be a marker for distinguishing bipolar depression from unipolar depression?

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ABSTRACT

Objective: We aimed to compare retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) thickness in bipolar disorder (BD) and major depressive disorder (MDD).

Method: The study included thirty MDD, thirty-two BD participants in depressive episode, and thirty-seven controls matched according to age, gender, body mass index (BMI), and smoking status. Optic coherence tomography (OCT) measurements were performed for both participants and controls. The RNFL and GCC thickness were measured and recorded automatically by a spectral OCT device. Participants were also subjected to Hamilton Depression Rating Scale (HAM-D).

Results: RNFL superior thickness was significantly lower in BD participants, compared to the MDD participants and controls ($p=0.001$). GCC inferior ($p=0.022$) and inferonasal ($p=0.005$) thickness were detected lower in BD group, compared to the control groups. In the BD group, HAM-D scores were negatively correlated with RNFL-temporal ($p=0.049$, $r=-0.357$), GCC inferotemporal ($p=0.02$, $r=-0.416$) and superotemporal thickness ($p=0.002$, $r=-0.546$).

Conclusions: RNFL thickness were lower in BD participants compared to the MDD and controls and, GCC thickness were lower in BD participants compared to the controls. Our findings support the hypothesis that neurodegeneration is part of the pathogenesis of BD. Future research are needed to confirm the lack of RNFL thickness in MDD, which could have immediate therapeutic consequences as well as implications for distinguishing BD from MDD.

KEY POINTS

- RNFL thickness is lower in BD participants compared to the MDD and controls.
- GCC thickness were lower in BD participants compared to the controls.
- HAM-D scores are negatively correlated with RNFL temporal and, GCC inferotemporal and superotemporal thickness.

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Bipolar disorder; major depressive disorder; optical coherence tomography; neurodegeneration

1. Introduction

It is difficult to distinguish depression in bipolar disorder (BD) from unipolar depression based only on clinical indicators [1]. However, the course, outcome, and treatment of two disorders are different. Providing an inappropriate antidepressant treatment to a bipolar depressive patient may lead to critical consequences including nonresponse, manic shift, rapid loss of drug efficacy, resistance to treatment and loss of time [2]. This challenging situation has led researchers to investigate biomarkers and neural markers which can be beneficial in differentiating these two conditions. Various neuroimaging studies have emphasized structural and functional differences in emotion, reward, and cognition-processing neural circuits between both depressive episodes [3]. In addition, many inflammatory and oxidative biomarkers point to differences between two depressive episodes [4]. However, to date, no reliable neural marker or biomarker has been found for identifying and monitoring these disorders.

The complexity and lack of clarity of the pathophysiology of mood disorders are among the main obstacles to finding a valid biomarker. In recent years, there has been a growing interest in neurodegeneration and neuroprogression as potential pathogenic factors associated with mood disorders [5]. The term 'neuroprogression' describes the pathological rearrangement of the central nervous system (CNS), which includes a reduction in plasticity and mild degenerative processes [6,7]. Neurodegeneration is characterized by gradual alterations in the motor, sensory, or cognitive neuronal populations that eventually become chronic and impair neuronal functions [6–8]. Neurodegenerative and neuroprogressive mechanisms involve multiple and complex interactions between the CNS, endocrine and immune systems, inflammatory processes, oxidative stress, neurotoxic proteins, and neuroplasticity [6–8].

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A growing number of Optical Coherence Tomography (OCT) studies offer another avenue for differentiating two disorder and exploring their pathophysiology [9]. This imaging technique is a non-invasive, in-expensive, rapid, and radiation-free method that measures the layers of retina and optic nerve which are considered as a direct extension of the brain [10,11]. Thinning in retinal layers are indicative of degenerative changes in the brain [9]. The retinal nerve fiber layer (RNFL) represents the axons and, ganglion cell complex represents three retinal layers: the nerve fiber layer, the ganglion cell layer (GCL), and the inner plexiform layer (IPL) thus, both represent an objective and sensitive parameter in the assessment of degeneration in neurological and psychiatric disorders [12].

Previous studies focusing on BD have reported a thinning in retinal nerve fiber and ganglion cell layer [9]. However, the results from Major Depressive Disorder (MDD) studies are controversial [13]. In addition, a recent meta-analysis has revealed a significant decrease in RNFL thickness in BD, but not in MDD [9]. Nonetheless, up to date, there is no direct comparison between MDD and BD in terms of OCT parameters. This current study aims to compare RNFL and GCC thickness of BD, MDD and healthy controls.

2. Materials and methods

2.1. Subjects and clinical assessments

This study is cross sectional and case-control research. The Ethics Committee of İzmir Democracy University Buca Seyfi Demirsoy Education and Research Hospital has approved the research protocol. All subjects were informed of the purpose of the study and provided documented informed consent. All investigations were conducted in strict adherence to the Declaration of Helsinki. This study included 30 UP and 32 BP depressive episode participants, who were diagnosed by two psychiatrists according to Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria in psychiatry department of İzmir Democracy University Medical Faculty. Sociodemographic data form was filled for all study groups, and Hamilton Depression Rating Scale (Ham-D) was applied to BP and UP participants.

2.2. Inclusion/exclusion criteria

Participants who had comorbid psychiatric disorders except tobacco use disorder; neurological, immunological, or systemic diseases (diabetes mellitus, hypertension, morbid obesity, etc.); and primary ophthalmological diseases such as glaucoma or retinal diseases were excluded. Participants with disorders that can affect the image quality or measurement values such as high refractive errors or cataract were also excluded. All participants were examined in Department of Ophthalmology and comprehensive examination including best corrected visual acuity (BCVA), intraocular pressure, slit lamb bio-microscopy, and fundus examination were performed. Participants and controls with normal eye findings (intraocular pressure (IOP) of lower than 21 mmHg, a refraction that is lower than 0.50 diopters both spherically and cylindrically, and no anterior or posterior segment pathologies as detected by slit lamp biomicroscopy) were included. To eliminate impact of age, sex and smoking on OCT measurements, groups were matched according to these parameters.

2.3. SD-OCT measurements

SD-OCT (DRI-OCT Triton, Topcon, Inc, Tokyo, Japan) measurements were performed to analyze RNFL and GCL (ganglion cell layer) thicknesses in peripapillary region. The images were evaluated blindly by the ophthalmologists in İzmir Democracy University Medical Faculty Department of Ophthalmology. RNFL thickness values were recorded in 4 quadrants and GCC thickness values were recorded in 6 sectors. To analyze these values in each group, SD-OCT device's automatic calculation and reporting system were used. The values of 4 quadrants (superior, temporal, inferior and nasal) for RNFL, and 6 sectors (superior, superotemporal, superonasal, inferior, inferotemporal, and inferonasal) for GCC were recorded. OCT measurements were conducted for both the right and left eyes across all participants. There were no significant differences between the right and left eye measurements. Only left eye measurements were analyzed to avoid additional complexity and to maintain clarity in our reporting.

3. Statistical methods

Statistical analyses were conducted using SPSS 25 (IBM Corporation, Armonk, New York, USA). Prior to comparisons, all data distributions were assessed using the Kolmogorov-Smirnov test. Categorical data were compared using the Pearson Chi-square test. Parametric tests (ANOVA and independent *t*-test) were employed for normally distributed data, while non-parametric tests (Kruskal–Wallis and Mann–Whitney *U*) were utilized for non-normally distributed data. A *p*-value of <0.05 was considered statistically significant for all tests.

4. Results

4.1. Socio-demographic data

The study included 30 MDD, 32 BD participants in depressive episode and 37 controls matched for age, gender, BMI, and smoking status. Mean age of the MDD, BD and control group was 43.70 ± 18.75, 40.68 ± 12.68 and, 40.02 ± 14.90 respectively. 22 (%73.3) of MDD, 16 (%50) of BD and, 21 of (%56.7) the control group were female. 10 of the UP participants (33.3%), 17 of the BP participants (53.2%) and 17 of the controls (54.1%) were smokers. Socio-demographic features of the groups are given in Table 1. The rate of married individuals was higher in the control groups and UP group compared to the BP group ($p = 0.002$).

4.2. Clinical data

In the MDD group, the mean year of the disease duration was 5.56 ± 5.04, the total number of depressive episodes was

1.76 ± 1.00 and, the mean HAM-D scores were 31.79 ± 10.34. The mean disease duration in BD participants was 15.30 ± 9.60, number of manic episodes was 7.76 ± 11.89, number of depressive episodes was 10.44 ± 14.28 and, the mean HAM-D scores were 23.00 ± 5.98. Table 1.

4.3. RNFL findings

While there was no difference between three groups in terms of RNFL inferior ($p = 0.530$) and RNFL nasal measurements ($p = 0.115$), RNFL temporal thickness was detected lower in BD group. But after Bonferroni correction this difference didn't reach the significance ($p = 0.041$). RNFL superior thickness was significantly lower in BD participants, compared to the MDD participants and controls ($p = 0.001$). Table 2.

4.4. GCC findings

GCC inferior ($p = 0.022$) and inferonasal ($p = 0.005$) thickness were detected lower in BD group, compared to the control groups. There was no difference between MDD and BD participants or MDD participants and control groups in terms of GCC inferior or inferonasal measurements ($p > 0.05$). There was no difference between groups in terms of GCC superior ($p = 0.338$), superonasal ($p = 0.085$), inferotemporal ($p = 0.186$) and superotemporal ($p = 0.344$). Table 2.

4.5. Correlations between disease severity and OCT parameters

In the BD group, HAM-D scores were negatively correlated with RNFL temporal ($p = 0.049$, $r = -0.357$), GCC inferotemporal ($p = 0.02$, r–0.416) and superotemporal thickness ($p = 0.002$, $r = -0.546$). Table 3. There was no correlation between HAM-D scores and OCT parameters in MDD group and there was no relationship between OCT measurements and disease duration in all participants ($p > 0.05$). Table 4.

5. Discussion

One of the most significant findings of the present study is lower RNFL superior thickness in BD participants, compared to MDD participants and healthy controls. Previous studies in MDD didn't find any difference in RNFL thickness compared to controls [14–16]. A recent metanalysis that evaluated quadrant-wise (superior, temporal, inferior and nasal) RNFL thickness also didn't find any difference in MDD [9]. Kalenderoglu et al. compared recurrent depressive and first attack depressive participants with healthy controls and found thinning in MDD participants' RNLF global measurements [11]. However, difference was no longer significant following Bonferroni correction. The authors of the study hypothesized that neurodegeneration starts in the ganglion cell nucleus and dendrites (GCL and IPL, respectively) and spreads to the axons forming the RNFL. Therefore, after disease progression, thinning would be detected in RNFL measurements. These hypotheses could also explain the lack of alterations in the RNFL measurements in our study and previous studies in MDD. As MDD participants in previous studies were mostly in their first episodes, their illness duration was short, and most had mild to moderate depression which all may affect neurodegeneration. In our study, mean years since the first episode were lower in MDD compared to the BD and nearly half of them were in the first episode. On the

Table 1. Comparison of the demographical and clinical features.

	UP (30) *n* (%)	BP (32) *n* (%)	Controls (37) *n* (%)	*p*
Age (mean ± SD)	43.70 ± 18.75	40.68 ± 12.68	40.02 ± 14.90	0.605[a]
Gender				0.157[b]
Female	22 (%73.3)	16 (%50)	21 (%56.7)	
Male	8 (%26.7)	16 (%50)	16 (%43.3)	
Marital status				0.002[b]
Married	16 (%53.3)	8 (%25)	25 (%67.5)	
Unmarried	14 (%46.7)	24 (%75)	12 (%32.5)	
Smoking				0.285[b]
Yes	10 (%33.3)	17 (%53.2)	17 (%45.9)	
No	20 (%66.6)	15 (%46.8)	20 (%54.1)	
BMI	23.39 ± 3.28	25.06 ± 2.83	23.45 ± 2.70	0.58
HAMD (mean ± SD)	31.79 ± 10.34	23.00 ± 5.98		0.001[c]
Years since first episode (mean ± SD)	5.56 ± 5.04	15.30 ± 9.60		0.000[c]
Number of depressive episodes (mean ± SD)	1.76 ± 1.00	10.44 ± 14.28		0.000[c]
Number of manic episodes (mean ± SD)		7.76 ± 11.89		

[a]ANOVA test; [b]Chi-square test; [c]Mann–Whitney *U* test.

Table 2. Comparison of the OCT parameters.

	UP	BP	Controls	*p*
	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	
RNLF-inferior	129.36 ± 20.91 µm	133.75 ± 24.96 µm	134.67 ± 13.44 µm	0.530[a]
RNLF-superior	137.5 ± 13.76 µm	121,00 ± 23.55 µm	134.1 ± 18.49 µm	**0.001**[b,c]
RNLF-nazal	84.96 ± 16.22 µm	77.90 ± 16.05 µm	84.02 ± 11.54 µm	0.115[a]
RNLF-temporal	81.1 ± 12.46 µm	74.18 ± 13.12 µm	80.59 ± 10.64 µm	**0.041**[a,d]
GCC-superior	108.03 ± 8.30 µm	105.34 ± 14.40 µm	109.72 ± 10.0 µm	0.338[b]
GCC-superonazal	116.3 ± 21.73 µm	115.40 ± 13.84 µm	122.40 ± 9.22 µm	0.085[b]
GCC-inferonasal	119.16 ± 8.74 µm	115.90 ± 11.96 µm	123.91 ± 8.96 µm	0. 014[b]
GCC-inferior	107.2 ± 7.53 µm	105.00 ± 9.59 µm	110.48 ± 7.63 µm	**0.025**[a,e]
GCC-inferotemporal	97.96 ± 9.41 µm	98.37 ± 8.37 µm	99.81 ± 13.14 µm	0.714[b]
GCC-superotemporal	95.1 ± 6.67 µm	94.28 ± 14.18 µm	97.10 ± 10.69 µm	0.833[b]

[a]ANOVA test; [b]Kruskal-Wallis test.
[c]The difference was between BP and control groups, also between BP and UP groups.
[d]There was no significant difference after *post-hoc*.
[e]The difference was between BP and control groups.

Table 3. Correlation between disease severity and OCT findings in BP patients.

		RNLF inferior	RNLF superior	RNLF nazal	RNLF temporal	GCC superior	GCC superonazal	GCC inferonasal	GCC inferior	GCC infero temporal	GCC supero temporal
Disease duration	Correlation coefficient	0.038	0.042	0.173	−0.022	0.032	0.020	,026	−0.001	−0.123	−0.032
	p Value	0.837	0.818	0.343	0.904	0.864	0.911	,886	0.995	0.503	0.861
HAM-D scores	Correlation coefficient	−0.321	−0.050	−0.012	−0.357	−0.458	−0.341	−0.284	−0.284	−0.416	−0.546
	p Value	0.078	0.789	0.949	**0.049**	**0.009**	0.061	0.122	0.122	**0.020**	**0.002**
Number of depressive episodes	Correlation coefficient	−0.098	0.088	0.104	−0.056	−0.160	−0.076	0.098	−0.082	−0.237	−0.281
	p Value	0.606	0.643	0.584	0.768	0.399	0.689	0.611	0.666	0.207	0.133
Number of manic episodes	Correlation coefficient	0.110	−0.030	0.359	0.134	0.296	0.313	0.387	0.289	0.070	0.096
	p Value	0.564	0.875	0.051	0.482	0.113	0.092	0.035	0.122	0.715	0.615

Spearman correlation test.

Table 4. Correlation between disease severity and OCT findings in up patients.

		RNLF inferior	RNLF superior	RNLF nazal	RNLF temporal	GCC superior	GCC supero nazal	GCC infero nasal	GCC inferior	GCC infero temporal	GCC supero temporal
Disease duration	Correlation coefficient	−0.097	0.006	−0.045	0.070	−0.203	−0.266	−0.175	−0.123	−0.225	−0.246
	p Value	0.644	0.976	0.831	0.739	0.331	0.199	0.354	0.558	0.280	0.236
HAM-D scores	Correlation coefficient	−0.210	−0.170	−0.027	−0.021	0.229	0.188	0.111	0.157	0.076	0.262
	p Value	0.273	0.379	0.889	0.916	0.231	0.330	0.566	0.415	0.695	0.170
Number of depressive episodes	Correlation coefficient	0.090	−0.018	0.03	0.249	-,0.17	−0.269	0.218	−0.265	−0.241	−0.322
	p Value	0.637	0.926	0.987	0.184	0.249	0.151	0.248	0.156	0.200	0.083

Spearman correlation test.

other hand, the majority of MDD participants in our study had moderate to severe depression and significantly higher HAM-D scores compared to the BD group. Unlike studies in MDD, reductions in the RNFL global measurements were consistently detected in BD [12,17,18]. In the meta-analysis mentioned above and in the first meta-analysis conducted on BD; significant reductions were detected in superior, inferior, and nasal quadrants of the RNLF; but not in temporal quadrant [9,19]. Consistent with previous studies we found significant thinning in RNFL superior measurements. However, RNFL thickness reduction can be associated with various neurological and ophthalmological conditions; considering this, we excluded such comorbidities. This careful approach may suggests that the observed reduction in RNFL indicates a specific association with BD. Determining whether neurodegeneration precedes the onset of bipolar disorder or vice versa is challenging, but the observed patterns imply that RNFL thinning might be indicative of underlying neurodegenerative processes that are part of the pathophysiology of BD, rather than a consequence of the disorder itself [6,8]. We can suggest that there is a greater neurodegeneration and progressive damage in BD than in MDD.

Another finding of our study is lower inferior and inferonasal GCC thickness in BD. Polo et al. reported thinning of GCC in the inferonasal and inferotemporal sectors [20]. Khalid et al. reported decreased average GCC in both eyes and in left superior and inferior sectors [12]. Our results are consistent with previous studies. However, comparing our results with relevant studies shows that GCC sector alteration varies. These variations might probably be reflecting a global loss of ganglion cells masked by the low statistical power due to a small sample size. In contrast, findings from MDD studies focused on GCL are inconsistent. Most of them reported a single cumulative value for the GC and IP layer (GCIPL) and found no significant difference [15,21]. One study measured GC and IP layers separately reported significantly lower GCL volumes more pronounced in recurrent depressions rather than first attack depressions reflecting progressive degeneration [11]. Our GCC findings are consistent with our RNFL findings suggesting neurodegeneration in BD. In addition, GCC sector measurements of MDD were numerically lower than controls and did not significantly differ from BD, may reflect a milder neurodegeneration in MDD.

There were significant differences regarding disease duration and the total number of mood episodes between bipolar and depression groups. Our results may reflect that BD group has more severe illness compared to the MDD group. These findings could be evaluated as confounding factor in our study. However, there was no correlation between RNFL, GCC thicknesses and disease duration or number of mood episodes in both groups. Our findings suggest higher neurodegeneration found in BD group may be associated with pathophysiology of the disorder rather than severity. We found negative correlation between HAM-D scores and RNFL temporal, GCC inferotemporal and, superotemporal measurements in BD group. In BD studies, negative correlation between RNFL, GCL-IPL [20–22] and disease severity parameters (illness duration, onset age, scale scores) have been

shown. However, none of the previous studies evaluated BD participants in active depressive phase. So one-to-one comparison with our study could not be possible. Considering our results, we can suggest that the episodes become more severe in BD with increased neurodegeneration.

Our study included participants with bipolar disorder and depression who were receiving a range of psychotropic medications, including antipsychotics, mood stabilizers (lithium, valproic acid), and antidepressants (SSRIs and SNRIs). Lithium is often cited for its neuroprotective properties, which have been associated with increases in grey matter volume in patients with bipolar disorder [23]. Conversely, valproic acid, while also considered neuroprotective, has been linked to decreased brain volume in epilepsy patients, which may suggest differential effects on neural structures depending on the disorder treated and the context of use [24]. Specifically, Kalenderoglu et al. noted that valproic acid users had a thinner Retinal Nerve Fiber Layer (RNFL) compared to non-users [20]. Furthermore, antidepressants, particularly SSRIs and SNRIs, have been observed to normalize changes in retinal parameters in patients with depression, as measured electrophysiologically [25]. Our study, however, was not specifically designed to isolate the effects of these medications on OCT measurements.

There are limitations should be acknowledged in our study. Firstly, the relatively small sample sizes may limit the generalizability of the results. Secondly, although the BD and MDD participants were matched in terms of age, gender, BMI, and smoking status, there is a significant difference in disease duration and severity, introducing additional complexity when comparing these groups, as the longer disease duration and more frequent depressive episodes in the BD group could confound the RNFL and GCC measurements. Lastly, the participants were receiving different groups of medications, including mood stabilizers, anti-depressants and anti-psychotic drugs which could also confound our findings.

Future longitudinal research is needed to confirm the lack of thinning in RNFL thickness in MDD. Moreover, head-to-head comparison between MDD and BD with larger samples matched in terms of disease duration, severity of depression, age of onset, BMI, comorbidities, smoking status, and gender should be conducted. Further studies should consider using Optical Coherence Tomography Angiography (OCTA), as it provides a unique and advanced visualization of blood flow in the retinal and choroidal circulations. This technology is particularly valuable when studying vascular changes that can vary due to neuroinflammatory processes during mood episodes. Xiao et al. (2024) demonstrated a decrease in macular vessel density in patients with Major Depressive Disorder (MDD), indicating the potential of OCTA to detect significant vascular alterations related to psychiatric disorders [26].

In conclusion we found lower RNFL thickness in BD participants compared to the MDD and controls and, found lower GCC thickness compared to the controls. We suggest that alterations in retinal layers could represent a trait marker rather than a state marker, indicating that thickness would not change according to the episodes of the disorders. According to our hypothesis, the changes in retinal nerve fiber layer and ganglion cell complex thickness in both MDD and bipolar disorder result from neurodegenerative processes. These structural changes are indicative of long-term pathophysiological processes rather than acute symptoms. Our findings support the hypothesis that neurodegeneration is part of the pathogenesis of BD. Quadrant and sector wise studies on OCT parameters may be beneficial for finding potential biomarkers in the diagnosis and monitoring of mood disorders.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data set of the research available at 'https://doi.org/10.5281/zenodo.11108256'.

References

[1] Stensland MD, Schultz JF, Frytak JR. Diagnosis of unipolar depression following initial identification of bipolar disorder. J Clin Psychiatry. 2008;69(5):749–758. doi: 10.4088/jcp.v69n0508.

[2] Ghaemi SN, Rosenquist KJ, Ko JY, et al. Antidepressant treatment in bipolar versus unipolar depression. Am J Psychiatry. 2004;161(1):163–165. doi: 10.1176/appi.ajp.161.1.163.

[3] Han KM, De Berardis D, Fornaro M, et al. Differentiating between bipolar and unipolar depression in functional and structural MRI studies. Prog Neuropsychopharmacol Biol Psychiatry. 2019;91:20–27. doi: 10.1016/j.pnpbp.2018.03.022.

[4] Lei X, Ren J, Teng X, et al. Characterizing unipolar and bipolar depression by alterations in inflammatory mediators and the prefrontal-limbic structural network. Depress Anxiety. 2023;2023:1–11. doi: 10.1155/2023/5522658.

[5] Palagini L, Geoffroy PA, Miniati M, et al. Insomnia, sleep loss, and circadian sleep disturbances in mood disorders: a pathway toward neurodegeneration and neuroprogression? A theoretical review. CNS Spectr. 2022;27(3):298–308. doi: 10.1017/S1092852921000018.
[6] Kapczinski NS, Mwangi B, Cassidy RM, et al. Neuroprogression and illness trajectories in bipolar disorder. Expert Rev Neurother. 2017;17(3):277–285. doi: 10.1080/14737175.2017.1240615.
[7] Tang SW, Helmeste DM, Leonard BE. Neurodegeneration, neuroregeneration, and neuroprotection in psychiatric disorders. Mod Trends Pharmacopsychiatry. 2017;31:107–123. doi: 10.1159/000470811.
[8] Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. 2011;35(3):804–817. doi: 10.1016/j.neubiorev.2010.10.001.
[9] Prasannakumar A, Kumar V, Mailankody P, et al. A systematic review and metaanalysis of optical coherence tomography studies in schizophrenia, bipolar disorder and major depressive disorder. World J Biol Psychiatry. 2023;24(8):707–720. doi: 10.1080/15622975.2023.2203231.
[10] Fujimoto JG. Optical coherence tomography for ultra-high resolution *in vivo* imaging. Nat Biotechnol. 2003;21(11):1361–1367. doi: 10.1038/nbt892.
[11] Kalenderoglu A, Çelik M, Sevgi-Karadag A, et al. Optic coherence tomography shows inflammation and degeneration in major depressive disorder patients correlated with disease severity. J Affect Disord. 2016;204:159–165. doi: 10.1016/j.jad.2016.06.039.
[12] Khalil DH, Said MM. Peripapillary retinal nerve fiber layer and ganglion cell complex degeneration in Egyptian patients with bipolar disorder. Eye. 2019;33(12):1852–1858. doi: 10.1038/s41433-019-0403-5.
[13] Clémence-Fau M, Schwan R, Angioi-Duprez K, et al. Retinal structural changes in mood disorders: the optical coherence tomography to better understand physiopathology? Prog Neuropsychopharmacol Biol Psychiatry. 2021;108:110080. doi: 10.1016/j.pnpbp.2020.110080.
[14] Yıldız M, Alim S, Batmaz S, et al. Duration of the depressive episode is correlated with ganglion cell inner plexifrom layer and nasal retinal fiber layer thicknesses: optical coherence tomography findings in major depression. Psychiatry Res Neuroimaging. 2016;251:60–66. doi: 10.1016/j.pscychresns.2016.04.011.
[15] Sönmez İ, 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(1):62–66. doi: 10.5152/npa.2015.10115.
[16] Schönfeldt-Lecuona C, Schmidt A, Kregel T, et al. Retinal changes in patients with major depressive disorder – a controlled optical coherence tomography study. J Affect Disord. 2018;227:665–671. doi: 10.1016/j.jad.2017.11.077.
[17] Garcia-Martin E, Gavin A, Garcia-Campayo J, et al. Visual function and retinal changes in patients with bipolar disorder. Retina. 2019;39(10):2012–2021. doi: 10.1097/IAE.0000000000002252.
[18] Polo V, Satue M, Gavin A, et al. Ability of swept source OCT to detect retinal changes in patients with bipolar disorder. Eye. 2019;33(4):549–556. doi: 10.1038/s41433-018-0261-6.
[19] Lizano P, Bannai D, Lutz O, et al. A meta-analysis of retinal cytoarchitectural abnormalities in schizophrenia and bipolar disorder. Schizophr Bull. 2020;46(1):43–53. doi: 10.1093/schbul/sbz029.
[20] Kalenderoglu A, Sevgi-Karadag A, Celik M, et al. Can the retinal ganglion cell layer (GCL) volume be a new marker to detect neurodegeneration in bipolar disorder? Compr Psychiatry. 2016;67:66–72. doi: 10.1016/j.comppsych.2016.02.005.
[21] Mehraban A, Samimi SM, Entezari M, et al. Peripapillary retinal nerve fiber layer thickness in bipolar disorder. Graefes Arch Clin Exp Ophthalmol. 2016;254(2):365–371. doi: 10.1007/s00417-015-2981-7.
[22] Gokcinar NB, Buturak SV, Ozkal F, et al. Optical coherence tomography neurodegenerative findings in patients with bipolar disorder. Asia Pac Psychiatry. 2020;12(4):e12394. doi: 10.1111/appy.12394.
[23] Ochoa EL. Lithium as a neuroprotective agent for bipolar disorder: an overview. Cell Mol Neurobiol. 2022;42(1):85–97. doi: 10.1007/s10571-021-01129-9.
[24] Sgobio C, Ghiglieri V, Costa C, et al. Hippocampal synaptic plasticity, memory, and epilepsy: effects of long-term valproic acid treatment. Biol Psychiatry. 2010;67(6):567–574. doi: 10.1016/j.biopsych.2009.11.008.
[25] Cosker E, Schwan R, Angioi-Duprez K, et al. New insights on the role of the retina in diagnostic and therapeutic strategies in major depressive disorder. Neurosci Biobehav Rev. 2020;113:262–272. doi: 10.1016/j.neubiorev.2020.03.006.
[26] Xu B, Li F, Zhang Z, et al. The use of optical coherence tomography (OCT) and OCT angiography in borderline personality disorder compared to health control subjects. CNS Neurosci Ther. 2024;30(3):e14699. doi: 10.1111/cns.14699.