

## Investigation of Retinal Biomarkers in Adult ADHD: A Comparative Optical Coherence Tomography Study

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### ABSTRACT

**Introduction:** Attention-deficit/hyperactivity disorder (ADHD) is increasingly recognized as a condition with both neurodevelopmental and neurodegenerative components. This study aims to investigate retinal structural alterations in adults diagnosed with ADHD using optical coherence tomography (OCT) and to identify potential retinal biomarkers.

**Methods:** The study included 31 adults diagnosed with ADHD according to DSM-5 criteria and 33 age- and sex-matched healthy controls. Retinal measurements were obtained from the right eye of all participants using the Spektralis® OCT system in accordance with the ETDRS protocol. Retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), ganglion cell complex (GCC), and central macular thickness (CMT) were measured. ADHD symptom severity was assessed using the Adult ADHD Self-Report Scale (ASRS). Group comparisons were made using independent t-tests, and correlations with clinical measures were evaluated using Pearson correlation analysis.

**Results:** Compared to healthy controls, the ADHD group showed a

statistically significant thinning in the CMT, IPL, and GCC layers, especially at the 1 mm zone ( $p < 0.05$ ). Mean values for the ADHD group versus the control group were as follows: CMT (254.3  $\mu\text{m}$  vs. 268.7  $\mu\text{m}$ ), IPL (35.2  $\mu\text{m}$  vs. 38.4  $\mu\text{m}$ ), and GCC (78.5  $\mu\text{m}$  vs. 82.3  $\mu\text{m}$ ). Similar thinning patterns were observed at the 3 mm zone for CMT and GCC, and at the 6 mm zone for IPL. No statistically significant differences were found in RNFL and GCL measurements. Thinning in specific retinal layers was significantly correlated with higher ADHD severity scores.

**Conclusion:** Our study demonstrates that adults with ADHD exhibit measurable retinal thinning, particularly in the CMT, IPL, and GCC layers. These structural changes may reflect underlying neurodegenerative processes and suggest that retinal imaging via OCT could serve as a useful non-invasive biomarker in adult ADHD.

**Keywords:** ADHD, central macular thickness, ganglion cell complex, inner plexiform layer, optical coherence tomography, retinal nerve fiber layer

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### INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is one of the neurodevelopmental disorders that can persist from childhood into adulthood or may emerge during adulthood. This neurodevelopmental disorder is characterized by symptoms such as inattention, impaired executive functions, excessive motor activity, and poor impulse control. It affects not only the daily quality of life of individuals but also various aspects of life, including career, social relationships, personal health, and psychological well-being (1). The diagnosis of ADHD still relies on subjective observations and self-reports by individuals. In adults, the diagnosis is often overlooked because symptoms that begin in childhood may attenuate with age. Additionally, the absence of a definitive biological marker or quantitative test for this disorder complicates the confirmation of the diagnosis. Since ADHD symptoms often do not show significant progression, individuals may not feel the need to seek medical help. This situation can lead to delays in the diagnostic process, resulting in negative impacts on the quality of life of affected individuals.

### Highlights

- There is significant thinning in CMT, IPL, and GCC in adults with ADHD.
- Thinning in CMT, IPL, and GCC correlates with ADHD symptom severity.
- There is no significant difference in RNFL and GCL thicknesses between groups.
- Retinal changes may reflect neurodegenerative processes in ADHD.
- OCT may serve as a potential biomarker tool in adult ADHD.

Recent neuroimaging studies suggest that ADHD may involve not only neurodevelopmental delays but also neurodegenerative components. Structural alterations, such as reduced gray matter volume in the prefrontal cortex, caudate nucleus, and cerebellum, have been observed in individuals with ADHD (2,3). These regions are closely linked to executive functions and attention regulation, and their involvement implies potential long-term neurobiological deterioration. Furthermore, dopaminergic dysregulation, commonly implicated in ADHD, is known to affect both cortical and subcortical brain structures, reinforcing the hypothesis that ADHD includes a progressive component in its pathophysiology.

In recent years, OCT has become an important research tool for examining the relationship between changes in retinal structure and primary psychiatric disorders. For example, changes in the retinal nerve fiber layer (RNFL) thickness in major depressive disorder have been proposed as a potential biomarker for the diagnosis of the disease (4–7). Similarly, changes in macular thickness in schizophrenia patients have been reported to be associated with disease-specific cognitive function loss (8–10). OCT offers several methodological advantages: it is non-invasive, fast, and easy to apply, making it particularly suitable for use in clinical populations such as individuals with ADHD. Furthermore, because the retina is considered a developmental and anatomical extension of the central nervous system, OCT allows for the high-resolution visualization of neuroretinal structures. This enables the detection of subtle neurodegenerative changes that may not be observable through conventional neuroimaging techniques. Previous research has also explored retinal structures in adults with ADHD using OCT. For instance, Erdoğan et al. (2021) found significant thinning in the ganglion cell layer and inner plexiform layer in adult ADHD patients, supporting the potential of OCT as a neurobiological tool in this population (11). These features highlight the potential value of OCT in understanding the neurobiological basis of psychiatric disorders and in contributing to the identification of early biomarkers. However, similar retinal alterations have also been reported in other psychiatric conditions such as major depressive disorder. This raises the question of whether the observed retinal thinning is specific to ADHD or part of a broader neuropsychiatric phenomenon.

The aim of this study is to examine the structural integrity of retinal layers in adult ADHD patients using OCT and to compare these findings with a healthy control group. Investigating the relationship between changes in retinal parameters such as central macular thickness (CMT), ganglion cell complex (GCC), and inner plexiform layer (IPL) and the severity of ADHD is of critical importance for understanding the neurodegenerative effects of this disorder on retinal structures. In our study, the relationship between Adult ADHD Self-Report Scale (ASRS) scores and OCT findings will be evaluated to explore the potential link between the clinical severity of ADHD and retinal neurodegeneration. The study seeks to address research gaps by evaluating retinal biomarkers' diagnostic and prognostic roles in ADHD. The findings may reveal that ADHD can affect not only the central nervous system but also retinal structures, thereby contributing to the development of new approaches in the diagnosis and treatment of this disorder.

## MATERIALS AND METHODS

### Participants

This study was conducted as a prospective design involving 31 adult ADHD patients who were diagnosed and followed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria at the Department of Psychiatry, Faculty of Medicine, Van Yuzuncu Yil University (1). Additionally, 33 healthy participants who presented to the eye clinic for routine eye examinations were included in the study. Data collection was carried out between March 2021 and February 2022, following approval from the ethics committee (Ethics

Committee approval date: 21/02/2020, no: 2020/04-32). All participants received study details and signed informed consent forms. This research was conducted in accordance with the principles outlined in the Declaration of Helsinki.

The patients in the ADHD group were randomly selected from those followed at the Department of Psychiatry, Faculty of Medicine, Van Yüzüncü Yıl University. Participants in the control group were matched with the patient group in terms of age and gender and were included only if they had no eye diseases besides refractive errors. Although measurements were obtained from both eyes of each participant, only the right eye was included in the analysis to avoid inter-eye correlation. This approach was based on prior studies using a similar methodology, and preliminary comparison within our sample revealed no significant differences between eyes. A detailed ophthalmological examination was performed for all participants. Posterior segment OCT images were obtained and recorded using the Spectralis® OCT (Heidelberg Engineering, Heidelberg, Germany).

### Participant Selection and Screening

The patient group consisted of volunteers aged 18–65 years. Adults diagnosed with ADHD but untreated in childhood were assessed thoroughly by psychiatrists. Through structured clinical interviews conducted by experienced psychiatrists, the presence of comorbid psychiatric or neurological disorders was systematically ruled out. These assessments ensured that only individuals meeting the DSM-5 criteria for ADHD without any additional psychiatric diagnoses or cognitive impairments were included in the study. All ADHD participants included in this study were newly diagnosed adults who had not previously received pharmacological treatment for ADHD. This ensured that retinal measurements were not confounded by prior or ongoing psychotropic medication use. However, the inclusion of only drug-naïve individuals may have biased the sample toward milder ADHD presentations. Participants were required not to be using medications for chronic diseases, have no history of substance or alcohol use disorders, and show no signs or diagnosis of neurodegenerative disorders. In terms of ocular criteria, participants were required to have spherical and/or cylindrical refractive error values of less than 1.5 D. Additionally, they should not have any eye diseases that could affect retinal thickness, such as glaucoma, uveitis, age-related macular degeneration, retinal vascular diseases, or cataracts. Furthermore, they should not have a history of eye surgery or ocular pathologies such as corneal disease or vitreous hemorrhage that could affect OCT imaging. Participants were also required to have no systemic diseases such as diabetes or hypertension that could affect eye health. Participants were not screened for other autoimmune or inflammatory conditions (e.g., undiagnosed multiple sclerosis) that may also influence retinal structure, which represents a limitation. The control group consisted of age- and gender-matched volunteers with no psychiatric disorders or ocular pathologies who presented to the hospital for routine check-ups.

### Sociodemographic Data Form

This form was used to collect detailed information about the sociodemographic characteristics and medical history of the participants. A questionnaire administered by an interviewer included personal information such as the participant's full name, date of birth, gender, marital status, and educational background. Additionally, information about the participants' medical conditions, diagnoses, duration of illness, treatments received, comorbid conditions, and family history was collected and systematically recorded. Information on alcohol use was collected as a binary variable (presence or absence), without assessing frequency or quantity. This approach was chosen to identify individuals with a history of any alcohol use rather than characterizing usage patterns.

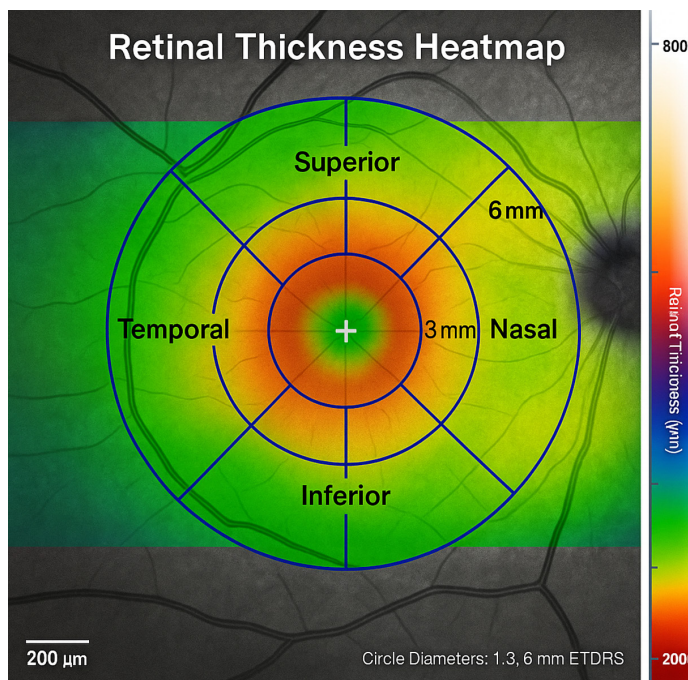
Adult ADHD Scale (ASRS): Developed under the auspices of the World Health Organization, the ASRS is a self-report scale designed

to assess ADHD symptoms in adults. The scale consists of 18 items, asking participants to respond to questions related to inattention and hyperactivity/impulsivity. Responses are recorded using a Likert-type scale ranging from 1 to 4 for each question. The Turkish adaptation of the ASRS scale was validated by Doğan et al. (12).

### Procedure

Adult individuals diagnosed with ADHD according to DSM-5 criteria and followed at the psychiatry clinic were informed about the study, and their informed consent was obtained. Diagnoses were confirmed through clinical interviews conducted by two board-certified psychiatrists, each with at least five years of clinical experience in adult ADHD. The evaluation was based strictly on DSM-5 diagnostic criteria. Sociodemographic data of the participants were recorded. Individuals who agreed to participate in the study were referred to the eye clinic. The eyes of all participants were dilated using mydriatic drops prior to OCT imaging. Imaging procedures were performed by a single experienced nurse (KK).

Optical coherence tomography (OCT) imaging was performed using the Spectralis® OCT device (Heidelberg Engineering, Heidelberg, Germany). During the scans, a fixation light was used, and patients were asked to focus on this light. The macular region was scanned according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Within this protocol, the macular region was defined by three concentric rings: the central 1 mm fovea, the parafoveal ring 1–3 mm from the umbo, and the perifoveal ring 3–6 mm from the umbo. These rings were divided to form nine quadrants, and thickness measurements in microns were recorded for each retinal layer (retinal nerve fiber layer [RNFL], ganglion cell layer [GCL], and inner plexiform layer [IPL]). The ganglion cell complex (GCC) was derived from the combined thickness of these three layers (Figure 1).



**Figure 1.** Retinal Thickness Heatmap Based on the ETDRS Protocol

This figure presents a color-coded heatmap of retinal thickness across the macular region, generated using spectral-domain optical coherence tomography (OCT) and structured according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. The macula is divided into three concentric rings: central foveal zone (1 mm), parafoveal ring (1–3 mm), and perifoveal ring (3–6 mm), further subdivided into four quadrants. Color gradients ranging from blue to red indicate relative retinal thickness, with cooler colors representing thinner regions and warmer colors indicating thicker areas. Average thickness values are displayed in micrometers ( $\mu\text{m}$ ) for each of the nine subfields. This standardized grid facilitates regional analysis of retinal integrity and comparison between clinical groups.

For each retinal layer, the average measurements from the 1 mm central fovea, 3 mm parafoveal ring, and 6 mm perifoveal ring were calculated. Specifically, the average of four sectoral measurements taken from the 3 mm parafoveal ring and 6 mm perifoveal ring was recorded. The total retinal thickness within the central 1 mm ring was recorded as the central macular thickness (CMT). All measurements were calculated separately for the patient and control groups and compared between the two groups. ADHD subtypes were not analyzed separately in this study, which limits insight into subtype-specific retinal differences. Measurements were taken from both eyes of all participants in the study, but only the right eyes were included in the analysis.

### Statistical Analysis

The study titled “Evaluation of Eye Health in Adult ADHD: Retinal Thickness Measurements Using OCT” was designed with a sample size determined to provide at least 80% power and a 5% Type 1 error rate for each variable. Sample size calculations were based on a predicted mean difference of approximately 10  $\mu\text{m}$  in retinal thickness between groups, with  $\alpha$  set at 0.05 and power ( $1-\beta$ ) at 0.80, informed by prior literature. Since the sample size was less than 50, the normality of continuous measurements in the study was assessed using the Shapiro-Wilk and Skewness-Kurtosis tests, and it was determined that the measurements followed a normal distribution. Therefore, parametric tests were applied. Descriptive statistics such as mean, standard deviation, number (n), and percentage (%) were presented for continuous variables. Independent t-tests were used to compare continuous measurement values between groups. Pearson correlation coefficients were calculated to determine the relationship between continuous measurement values. Chi-square tests were used to determine the relationship between gender and group. To control for Type I error due to multiple comparisons across nine retinal regions, Bonferroni correction was applied, setting the adjusted significance threshold at  $p < 0.0056$  ( $0.05/9$ ). A p-value of  $< 0.05$  was used as the statistical significance level, and IBM SPSS for Windows, version 26, was used as the statistical software package.

### RESULTS

When examining the demographic and sociodemographic characteristics of the adult ADHD and control groups, the groups were statistically matched in terms of various parameters such as age, gender, education level, marital status, employment status, monthly income level, smoking, and alcohol use. No statistically significant differences were found between the groups for any parameter ( $p > 0.05$ ), indicating successful matching. The mean age of participants was  $27.21 \pm 3.58$  years in the control group and  $25.42 \pm 4.00$  years in the ADHD group, with no significant difference between the groups ( $p = 0.063$ ). Additionally, the gender distribution was balanced in both groups, with similar male-to-female ratios ( $p = 0.985$ ). The similar sociodemographic profiles of the groups enhance the validity of subsequent analyses by reducing the influence of potential confounding variables (Table 1).

Optical coherence tomography (OCT) measurements conducted between the ADHD and control groups revealed significant structural differences in retinal layers. In the evaluation of central macular thickness (CMT), significant thinning was observed in the ADHD group at 1 mm and 3 mm measurements ( $p < 0.05$ ), suggesting that ADHD may be associated with structural changes in the macular region. However, no significant difference was observed between the groups at 6 mm measurements ( $p = 0.210$ ). In the examination of the inner plexiform layer (IPL), significant thinning was detected in the ADHD group compared to the control group at 1 mm and 6 mm measurements ( $p < 0.05$ ), indicating that ADHD may be associated with structural alterations in the IPL that could reflect underlying neurobiological processes. However, no significant difference was found between the two groups at 3 mm measurements ( $p = 0.085$ ).

**Table 1.** Demographic and Sociodemographic Characteristics of ADHD and Control Groups

Parameter	Control Group (n: 33)	Study Group (n: 31)	p-value
Mean Age, Mean ± SD (years)	27.21 ± 3.58	25.42 ± 4.00	0.063
Gender, n (%)			0.985
- Female	16 (51.6%)	15 (48.4%)	
- Male	17 (51.5%)	16 (48.5%)	
Educational Level, n (%)			0.921
- High school or below	12 (36.4%)	11 (35.5%)	
- Bachelor's degree	14 (42.4%)	13 (41.9%)	
- Master's or doctoral degree	7 (21.2%)	7 (22.6%)	
Marital Status, n (%)			0.942
- Single	22 (66.7%)	21 (67.7%)	
- Married	11 (33.3%)	10 (32.3%)	
Employment Status, n (%)			0.874
- Employed	20 (60.6%)	19 (61.3%)	
- Unemployed/Student	13 (39.4%)	12 (38.7%)	
Monthly Income Level, n (%)			0.910
- Low	10 (30.3%)	9 (29.0%)	
- Middle	15 (45.5%)	14 (45.2%)	
- High	8 (24.2%)	8 (25.8%)	
Smoking Status, n (%)			0.962
- Smoker	9 (27.3%)	8 (25.8%)	
- Non-smoker	24 (72.7%)	23 (74.2%)	
Alcohol Use, n (%)			0.951
- Yes	7 (21.2%)	6 (19.4%)	
- No	26 (78.8%)	25 (80.6%)	

**Statistical Tests:** Chi-square test for categorical variables; Independent samples t-test for continuous variables.  
SD: Standard deviation.

In the evaluation of the ganglion cell complex (GCC), significant thinning was observed in the ADHD group at 1 mm and 3 mm measurements ( $p < 0.05$ ), supporting the notion that ADHD may be associated with structural differences in the GCC. However, no significant difference was observed at 6 mm measurements ( $p = 0.150$ ) (Table 2).

Similarly, the inner plexiform layer (IPL) showed significant thinning in the ADHD group at 1 mm and 6 mm ( $p < 0.05$ ), while the 3 mm measurement did not reach statistical significance ( $p = 0.085$ ). In the ganglion cell complex (GCC), thickness was significantly reduced in the ADHD group at 1 mm and 3 mm ( $p < 0.05$ ), with no significant difference at 6 mm ( $p = 0.150$ ) (Table 2).

No significant differences were found between groups in the ganglion cell layer (GCL) or the retinal nerve fiber layer (RNFL) at any of the measured zones (1 mm, 3 mm, or 6 mm) ( $p > 0.05$ ). These results indicate regional variations in retinal thickness in the ADHD group, particularly localized to the macular and parafoveal zones.

In the ADHD group, ASRS scores were categorized as low (0–30), moderate (31–45), and high (46–72). As ASRS scores increased, significant reductions in CMT, GCC, and IPL thicknesses were observed, especially at 1 mm measurements ( $p < 0.001$ ). At the 3 mm zone, CMT and GCC values declined with higher ASRS scores ( $p < 0.05$ ), while IPL thickness did not differ significantly ( $p = 0.085$ ). At the 6 mm zone, IPL thickness showed a significant negative correlation with ASRS scores ( $p = 0.035$ ), while CMT and GCC did not ( $p > 0.05$ ) (Table 3).

## DISCUSSION

In this prospective study, the retinal structures of individuals diagnosed with adult-type ADHD were examined using optical coherence

tomography (OCT) and compared with a healthy control group. The findings revealed significant thinning in central macular thickness (CMT), inner plexiform layer (IPL), and ganglion cell complex (GCC) thicknesses in individuals with ADHD. Given that all participants with ADHD were newly diagnosed and had not received any prior pharmacological treatment, the observed structural alterations in the ganglion cell complex (GCC) and inner plexiform layer (IPL) are unlikely to be attributable to psychopharmacological agents. This methodological feature strengthens the argument that the retinal changes observed in our study are more likely to reflect intrinsic neurobiological alterations associated with ADHD itself, rather than being secondary to treatment effects. Rather than suggesting a definitive biomarker, our findings indicate that OCT parameters such as CMT, IPL, and GCC may offer preliminary insight into structural alterations potentially associated

This finding is consistent with the growing body of neurobiological research indicating that ADHD is not solely a neurodevelopmental disorder but also involves subtle neurodegenerative components. Neuroimaging studies have shown volumetric reductions in brain regions such as the prefrontal cortex, basal ganglia, and cerebellum—areas implicated in attention regulation and executive function (13,14). These structural abnormalities are thought to reflect disrupted dopaminergic and noradrenergic signaling pathways, which also play a critical role in retinal function (15). Notably, the inner retinal layers, including the ganglion cell complex and inner plexiform layer, are densely innervated by dopaminergic amacrine cells, making them potential targets for dopaminergic dysregulation in ADHD (16). Therefore, the observed thinning in GCC and IPL in our ADHD cohort may serve as a peripheral indicator of central dopaminergic dysfunction, bridging the gap between retinal structural changes and the broader neurobiological underpinnings of ADHD. These observations should be interpreted with caution and in the context of other psychiatric research findings.

**Table 2.** Comparison of Retinal Layer Thicknesses Between ADHD and Control Groups

Parameter	Control Group (n: 33)	Study Group (n: 31)	*p-value
<b>CMT (Central Macular Thickness, <math>\mu\text{m}</math>)</b>			
- 1 mm	265.32 $\pm$ 16.45	255.21 $\pm$ 15.12	<b>0.009</b>
- 3 mm	260.14 $\pm$ 15.89	252.67 $\pm$ 14.78	<b>0.018</b>
- 6 mm	255.45 $\pm$ 15.23	250.34 $\pm$ 14.45	0.210
<b>IPL (Inner Plexiform Layer, <math>\mu\text{m}</math>)</b>			
- 1 mm	20.45 $\pm$ 3.34	18.23 $\pm$ 2.12	<b>0.008</b>
- 3 mm	19.89 $\pm$ 3.23	18.45 $\pm$ 2.12	0.085
- 6 mm	19.12 $\pm$ 3.12	17.78 $\pm$ 2.01	<b>0.035</b>
<b>GCC (Ganglion Cell Complex, <math>\mu\text{m}</math>)</b>			
- 1 mm	47.32 $\pm$ 8.45	43.21 $\pm$ 7.12	<b>0.012</b>
- 3 mm	46.14 $\pm$ 8.89	42.67 $\pm$ 7.78	<b>0.022</b>
- 6 mm	45.45 $\pm$ 8.23	41.34 $\pm$ 7.45	0.150
<b>GCL (Ganglion Cell Layer, <math>\mu\text{m}</math>)</b>			
- 1 mm	14.48 $\pm$ 3.62	13.10 $\pm$ 2.49	0.081
- 3 mm	14.12 $\pm$ 3.45	12.89 $\pm$ 2.34	0.120
- 6 mm	13.78 $\pm$ 3.23	12.45 $\pm$ 2.12	0.250
<b>RNFL (Retinal Nerve Fiber Layer, <math>\mu\text{m}</math>)</b>			
- 1 mm	12.00 $\pm$ 1.71	11.77 $\pm$ 1.78	0.607
- 3 mm	11.89 $\pm$ 1.65	11.45 $\pm$ 1.58	0.450
- 6 mm	11.45 $\pm$ 1.52	11.12 $\pm$ 1.45	0.320

Statistical significance based on the results of independent samples t-tests. A p-value of less than 0.05 was considered statistically significant.

CMT: Central Macular Thickness; GCC: Ganglion Cell Complex; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; RNFL: Retinal Nerve Fiber Layer

**Table 3.** Correlation Between ASRS Scores and OCT Parameters in the ADHD Group (n: 31)

Parameter	ASRS Score (Low)	ASRS Score (Medium)	ASRS Score (High)	*p-value	Correlation (r)
<b>CMT (Central Macular Thickness, <math>\mu\text{m}</math>)</b>					
- 1 mm	245.32 $\pm$ 8.45	238.21 $\pm$ 7.12	230.45 $\pm$ 6.78	<b>&lt;0.001</b>	-0.72
- 3 mm	240.14 $\pm$ 7.89	235.67 $\pm$ 6.78	228.34 $\pm$ 6.45	<b>0.012</b>	-0.55
- 6 mm	235.45 $\pm$ 7.23	232.34 $\pm$ 6.45	230.12 $\pm$ 6.23	0.210	-0.18
<b>GCC (Ganglion Cell Complex, <math>\mu\text{m}</math>)</b>					
- 1 mm	95.32 $\pm$ 4.45	90.21 $\pm$ 4.12	85.45 $\pm$ 3.78	<b>&lt;0.001</b>	-0.75
- 3 mm	92.14 $\pm$ 4.89	88.67 $\pm$ 4.78	84.34 $\pm$ 4.45	<b>0.008</b>	-0.58
- 6 mm	89.45 $\pm$ 4.23	87.34 $\pm$ 4.45	85.12 $\pm$ 4.23	0.150	-0.22
<b>IPL (Inner Plexiform Layer, <math>\mu\text{m}</math>)</b>					
- 1 mm	45.67 $\pm$ 2.34	42.23 $\pm$ 2.12	38.45 $\pm$ 2.01	<b>&lt;0.001</b>	-0.70
- 3 mm	44.89 $\pm$ 2.23	43.45 $\pm$ 2.12	41.89 $\pm$ 1.98	0.085	-0.30
- 6 mm	43.12 $\pm$ 2.12	40.78 $\pm$ 2.01	38.45 $\pm$ 1.89	<b>0.035</b>	-0.42

Statistical significance based on the results of one-way ANOVA and Pearson correlation analysis. ASRS scores were categorized as Low ( $\leq 30$ ), Medium (31-50), and High ( $\geq 51$ ).

ASRS: Adult ADHD Self-Report Scale; CMT: Central Macular Thickness; GCC: Ganglion Cell Complex; IPL: Inner Plexiform Layer; OCT: Optical Coherence Tomography

The retina is considered an extension of the central nervous system and can be directly affected by neurodegenerative processes (17). The retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL) play a critical role in transmitting visual information to the brain (18). In this study, significant thinning was observed in CMT, IPL, and GCC thicknesses in the ADHD group, while no significant differences were found between the groups in RNFL and GCL thicknesses. The literature includes studies reporting reduced RNFL thickness in children with ADHD (19). However, the absence of significant differences in RNFL thickness in the adult ADHD group in our study suggests that the retinal effects of ADHD may vary by age group. Additionally, the retinal changes observed in adults with ADHD may be influenced by factors such as

the chronic course of the disease and treatment history, indicating that the neurobiological mechanisms of ADHD may change with age. These findings are partially aligned with a recent study by Tünel and Şahinoğlu Keşkek (2023), which reported significantly lower RNFL, CMT, and GCC thicknesses in adults with ADHD compared to controls, suggesting potential structural alterations across multiple retinal layers (20). Their study also supports the view that OCT-derived parameters could offer supplementary insight into the neurobiological underpinnings of adult ADHD.

CMT thinning in the ADHD group was most marked at 1 mm and 3 mm zones. This suggests ADHD may alter macular structure, linked to

symptom severity. Similarly, the reduction in IPL and GCC thicknesses suggests that ADHD may have neurodegenerative effects on retinal neuronal structures. In particular, the reduction in GCC thickness may indicate damage to ganglion cell axons, which could increase the risk of impaired visual function in individuals with ADHD. These findings demonstrate that ADHD may affect not only the central nervous system but also retinal structures.

One of the most important findings of our study is the significant correlation between ADHD severity and thinning in retinal layers. Specifically, as ASRS scores increased in the ADHD group, significant reductions were observed in central macular thickness (CMT), ganglion cell complex (GCC), and inner plexiform layer (IPL) thicknesses. This finding indicates that the effects of ADHD on retinal structures are not limited to structural changes but are also directly related to the clinical severity of the disorder. The significant reduction in CMT, GCC, and IPL thicknesses observed at 1 mm measurements suggests that the effects of ADHD on retinal structures may be more pronounced in the macular region. These results suggest that the effects of ADHD on retinal structures may follow a gradient decreasing from the center to the periphery and may be more pronounced in the perimacular region.

In conclusion, this study demonstrates significant changes in retinal structures in adults with ADHD. In particular, the reduction in CMT, GCC, and IPL thicknesses suggests that ADHD may have neurodegenerative effects on retinal structures. These findings provide important insights into the neurobiological basis of ADHD. Additionally, the correlation between thinning in retinal layers and ADHD severity indicates that the effects of this disorder on retinal structures may be a dynamic process.

The literature includes studies examining the effects of ADHD on retinal structures, but most of these studies have focused on pediatric populations and have not thoroughly investigated the relationship between retinal changes and clinical severity. For example, a meta-analysis by Li et al. (2021) found a significant association between ADHD and retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thickness in children (21). Similarly, studies by Hergüner et al. (2018) and Kaymak et al. (2021) reported reduced nasal RNFL thickness in children with ADHD (19,22). However, Kaymak et al. (2021) did not find a significant correlation between RNFL thickness and ADHD severity (22). In contrast, our study found no significant differences in RNFL thickness in the adult ADHD group. This finding suggests that the retinal effects of ADHD may vary by age group.

A study by Ayyildiz et al. (2020) found no significant differences in RNFL thickness and macular thickness between children and adolescents with ADHD and the control group (23). This finding is consistent with the absence of significant differences in RNFL thickness in the adult ADHD group in our study. However, significant thinning was observed in CMT, IPL, and GCC thicknesses in our study. These findings suggest that the effects of ADHD on retinal structures may be selective and more pronounced in the macular region.

### Contribution to the Literature and Recommendations

Our study is one of the first to thoroughly examine the relationship between ADHD severity and retinal structures and to evaluate this relationship using a clinical severity scale such as the ASRS. These findings demonstrate that the effects of ADHD on retinal structures are not limited to structural changes but are also directly related to the clinical severity of the disorder. Therefore, the examination of retinal structures may serve as an important tool for understanding the neurobiological basis of ADHD and assessing the severity of the disorder.

Additionally, the findings of our study suggest that the effects of ADHD on retinal structures may be a dynamic and progressive process. However,

further studies with larger sample sizes and longer durations are needed to confirm these findings and better understand the retinal effects of ADHD.

### Limitations

Several limitations of this study should be acknowledged. First, the sample size was relatively small ( $n = 31$  ADHD,  $n = 33$  control), which may limit the generalizability of the findings. Although the study was statistically powered to detect moderate effects, larger-scale studies are needed to confirm these results across broader populations. Second, appropriate corrections for multiple comparisons were applied using the Bonferroni method to minimize the risk of Type I error, particularly across nine retinal subregions. Third, while comorbid psychiatric and neurological disorders were systematically ruled out using structured clinical interviews, participants were not screened for other subclinical autoimmune or inflammatory conditions (e.g., undiagnosed multiple sclerosis), which could confound retinal findings. Fourth, although data were collected from both eyes, only right eye was included in the analysis to maintain consistency with previous research and avoid statistical dependency; within-sample comparisons showed no significant difference between eyes. Additionally, although a regression analysis adjusting for age and gender was considered to better explore the association between ASRS scores and retinal thickness, the relatively small sample size ( $n = 31$ ) posed a risk of overfitting. Therefore, Pearson correlation was used as the primary method. We acknowledge that regression analysis with adequate statistical power could offer a more robust model and recommend this for future research. Fifth, ADHD subtypes were not differentiated in the analysis, which may obscure subtype-specific retinal characteristics. Finally, as a cross-sectional study, the findings cannot establish causal relationships between ADHD and retinal changes. Future longitudinal research is required to explore the progression and temporal dynamics of these structural alterations.

In conclusion, our study makes a significant contribution to the literature as one of the first to demonstrate the relationship between ADHD severity and retinal structures. At this stage, retinal thinning cannot be considered a diagnostic marker for ADHD, but it may contribute to a better understanding of the disorder's neurobiological correlates. These findings represent an important step in understanding the effects of ADHD on retinal structures and developing new approaches for the diagnosis and treatment of this disorder.

**Ethics Committee Approval:** Approval was obtained from the Van Yuzuncu Yil University Faculty of Medicine Clinical Research Ethics Committee dated February 21, 2020, with decision number 2020/04-32.

**Peer Review:** Externally Peer-Reviewed.

**Informed Patient Consent:** Participants were informed about the purpose of the study, and their written informed consent was obtained.

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**Data Availability Statement:** The data supporting the findings of this study are available from the corresponding author upon reasonable request. All data have been anonymized and prepared in compliance with ethical standards to ensure participant confidentiality. We are committed to promoting transparency and reproducibility in research, and access to the data will be provided for academic and non-commercial purposes.

**Author Contributions:** Concept- FK; Design- ST, FK; Supervision- ST, FK; Source- ST, FK; Data Collection and/or Processing- ST; Analysis and/or Interpretation-- ST, FK; Literature Search- FK; Writing- FT; Critical Reviews- ST, FK.

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