RESEARCH ARTICLE

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Retinal Scan with Optical Coherence Tomography in Adult Attention Deficit Hyperactivity Disorder

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SUMMARY

Objective: In this study, the retinal nerve fiber layer (RNFL) thicknesses were compared between adult attention deficit hyperactivity disorder (ADHD) cases and healthy controls.

Method: The study included adults diagnosed with ADHD based on the DSM-5 criteria and age and gender matched healthy controls. Spectral area optical coherence tomography (OCT) was performed on the 52 eyes of 26 participants with ADHD and the 52 eyes of the 26 healthy control individuals.

Results: Comparing the data on the 52 eyes of 26 ADHD participants and the 52 eyes of 26 healthy control participants indicated that the central macular thickness (CMT) and the RNFL thicknesses, the ganglion cell complex (GCC), the mean inner macular ring (MIR-AVG) and the mean outer macular ring (MOR-AVG) thicknesses were significantly lower in the ADHD group.

Conclusion: This is the first study in the literature on the RNFL thickness in adult ADHD patients. Our findings demonstrated that RNFL thickness is lower in ADHD cases as the unmyelinated axons are reduced in ADHD. Hence, the quantitative and reproducible nature of Spectral Domain-OCT thickness measurements can be used as biomarkers to monitor disease progression in ADHD cases.

Keywords: ADHD, adult, optical coherence tomography, retinal nerve fiber thickness

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD), characterized by inattention, hyperactivity and impulsivity is one of the most common psychiatric disorders in childhood and adolescence. It affects 8% to 12% of children in the world and symptoms can continue into adulthood. The aetiology of ADHD is still unknown and there is not an accepted imaging method for investigating ADHD (Thapar 2016, Biederman and Spencer 1999).

Understanding the biological basis of psychiatric disorders is made dificult by the methodological limitations of studying the live human brain. Recently, optical coherence tomography (OCT) has been used as a means of indirectly evaluating human brain functions. OCT is a non-invasive imaging method with an operating system similar to that of ultrasonography. It enables evaluation of the retinal structures such as the retinal nerve fiber thickness (RNFL), macular volume and macular thickness. Given the developing technology, structures such as the retinal layers, retinal nerve fiber layer (RNFL) and choroidal layer can be examined in detail with OCT (Dickmann et al. 2012).

The retina is anatomically and developmentally an extension of the central nervous system which can reflect changes occurring in the brain such that powerful information about the panoramic image of the brain is obtained by examining the retina. Neurodegenerative diseases are known to be associated with retina neuron loss (London at al. 2013). In studies using OCT, the loss of retinal ganglion cells has been shown in Parkinson's disease, Alzheimer's disease, and Multiple Sclerosis (Inzelberg at al. 2004, Lu et al. 2010, Petzold et al. 2010). Recently increased interest on the possibility of similar changes in psychiatric disorders has demonstrated RNFL and macular thinning in various

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psychiatric disorders including schizophrenia (Ascaso et al. 2015, Mehraban et al. 2016).

ADHD is associated with somatomotor and visual network dysfunctions as well as high-level cognitive-behavioral problems (Cortese et al. 2012). Neurotransmitters such as dopamine, glutamate and GABA are also essential for post-ocular structures such as the thalamus and visual cortex, next to the retinal functions (Silverstein and Rosen 2015). Decreased GABA and increased glutamate levels in the prefrontal cortex (PFC) and striatum have been demonstsrated together with the dopaminergic dysregulation in ADHD (Edden et al. 2013, Moore et al. 2006). It has been reported that dopamine has a multi-trophic role for retinal functions and that glutamate acts as a neurotoxin causing destruction of retinal ganglion cells (Sucher et al. 1997, Witkovsky 2004).

Significant loss of RNFL thickness was found in Parkinson's disease with lowered dopamine levels (Inzelberg et al. 2004). Also, retinal layer thinning was shown in adults with Restless Legs Syndrome (RLS) which is highly comorbid with ADHD and also shares a common pathophysiology with Parkinson's disease (Cortese et al. 2008, Köse et al. 2019). The decrease in peripapillary RNFL in bipolar disorder was determined to be related to disease duration, and increased RNFL thinning was demonstrated in the chronic periods of schizophrenia when dopamine levels are lowered (Lee at al. 2013, Mehraban et al. 2016).

During literature survey we saw that there were only few paediatric studies with conflicting results on retinal examination by OCT in ADHD (Bae at al. 2019, Hergüner et al. 2018). Considering the length of exposure and symptom persistence in adult ADHD, it was thought that retinal changes in adults may differ from those seen in children. Hence, it was aimed in this study to compare the results of OCT investigation in adult ADHD patients and healthy controls, expecting that retinal changes indicating ADHD-related neuropathology are present and measurable in adult ADHD cases.

METHOD

This prospective study, conducted in Başkent University Adana Dr. Turgut Noyan Hospital psychiatry outpatient clinic, was started in June 2019 by preplanning on the basis of power analysis to enroll a minimum of 23 ADHD patients and completed in October 2019. The study was approved by Başkent University Faculty of Medicine Clinical Research Ethics Committee and written consents were obtained from all participants.

Inclusion criteria of the study comprised volunteering to participate, literacy, being in the age range of 18-64 years, not having any known mental illness or mental retardation, organic and / or neurological disease that could impair cognitive functions and being on continuous use of medication. Suitability of each participant with the inclusion criteria of the study was ascertained through a detailed examination by a specialist in adult psychiatry. Medical records of the patients and the control group were examined and patients with diagnoses of known organic diseases and psychiatric disorders were excluded from the study. Also, patients with glaucoma, previous eye surgery, uveitis and retinal disease were not included in the study.

The participant group of the study was selected from the patients consulting our outpatient clinic with symptoms of inability to concentrate, inattention, irritability, forgetfulness, anxiety and depression. Patients scoring 36 on the Wender-Utah Rating Scale (WURS) were invstigatied for ADHD on the basis of the DSM-5 diagnostic criteria. Those having a comorbid psychiatric disorder or a history of paediatric ADHD diagnosis with psychostimulant therapy over the previous 6 months were excluded from the study. Patients aged ≥18 years and attending educatioin was started with the planned pharmacotherapy after investigation by OCT.

The final 52 study participants consisted of 26 individuals with ADHD-Combined diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders and 26 healthy individuals compatible with the inclusion criteria and age and gender matched with the ADHD group, recruited either from the hospital staff or from visitors to the polyclinic.

OCT Measurements

The OptovueRTVue 100-2 (Optovue, Fremont, CA, USA), a Spectral Domain OCT devce, was used for the OCT measurements. Retinal nerve fiber thickness and the retinal nerve fiber layer measurements were made by using the optic nerve head protocol over a ring area with a diameter of 3.45 mm surrounding the optic nerve head after dilating the pupils with 1% tropicamide to ensure reliable measurements. Measurements with the signal strength of ≥6 were included in the analyses. The software of the OCT device measured automatically the average RNFL in each and all quadrants in the 'The Early Treatment Diabetic Retinopathy Study' (ETDRS) chart. Retinal nerve fiber thickness was examined in the four quadrants and the average RNFL thickness was included in the analyses. In the macular area, the central macular thickness (CMT) and also the retinal thickness of the inner ring and the outer rings, depicted in four quadrants, were measured and noted. Macular thickness maps were created automatically by the software after radial linear scans centered on the fovea. Ganglion cell complex (GCC) measurement included 15 vertical line sections in a 7-mm square area 1 mm temporal to the foveal center.

Data Acquisition Tools

The Sociodemographic Data Form: This is a questionnaire developed by the researchers for determining the sociodemographic characteristics of the participants.

The Wender-Utah Rating Scale (WURS): The WURS was developed as a 61- item scale to measure in adults the presence and severity of ADHD symptoms and signs of childhood. The original WURS was later shortened to a 5-point Likert-type self-report scale to include the 25 items that enabled the best differentiaton of ADHD patients from the control group, with each item scored between 0 and 4 points. The validity and reliability of the the Turkish language version of the WURS with a cut-off score set at 36 was reported by Öncü et al. (2005).

Statistical Analysis

The SPSS 23.0 package program was used for statistical analysis of the data. Categorical measurements were shown in numbers and percentages, and continuous measurements were expressed in terms of the mean, the standard deviation and the median with the minimum–maximum range. Categorical variables were compared using the Fisher's exact test. Distributions of the continuous measurements were checked for the inter-group comparisons and the Student T was used for variables showing parametric distribution. Correlations between parameters were analyzed using the Pearson Correlation test. The correlation coefficient between variables was ranked as high for $r \geq 0.91$, good for $0.90 \leq r \geq 0.71$, moderate for $0.70 \leq r \geq 0.51$, low for $0.50 \leq r \geq 0.31$and as nil for $r \leq 0.3$. Statistical significance level was taken as 0.05 in all tests. Multivariate logistic regression analysis was used to measure the effect of age and other parameters.

RESULTS

The patient groups included 14 (53.8%) females and 12 (46.2%) males with a median group age of 33.58 years. The control group included 18 (69.2%) females and 8 (30.8%) males with a median group age of 32.69 years. The two groups did not differ significantly on the basis of age (p=0.774) and gender (p=0.393).

The OCT measurements of RNFL thickness, central macular thickness, the ganglion cell complex, the mean thicknesses of the inner and outer macular rings, and the thicknesses in each of the four quadrants were found to be significantly lower in the ADHD group ($p<0.05$ for all parameters) (Table 1).

The OCT measurements of GCC-AVG, MIR-AVG, MIR-SUP, MIR-TEM, MOR-AVG, MOR-INF and MOR-TEM decreased with increasing age, showing statistically significant negative correlations with the age variable in the ADHD group (Table 2a). Similarly significant correlations were not found between these parameters and the age variable in the control group (Table 2b).

In the Logistic Regression analysis using the Backward-Wald method, ADHD (0=yes / 1=no) was taken as the dependent group; and the age, gender and retinal layer measurements were added to the model as independent variables to identify the risk factors affecting ADHD. The Backward-Wald method enables determining the real independent risk factors by excluding from the model the independent variables that

Table 1. Retinal Nerve Fiber, Ganglion Cell Complex and Macular Thickness Values of The ADHD and The Control Groups

	Control (n=26)		ADHD group (n=26)		
	Mean	Std. Deviation	Mean	Std. Deviation	P
RNFL-AVG	113.23	9.9	104.98	8.5	0.0001
GCC	99.27	5.5	95.40	6.0	0.001
CMT	245.96	16.1	236.79	19.0	0.009
MIR-AVG	316.08	11.2	306.73	17.4	0.001
MIR-SUP	322.90	13.7	312.40	17.9	0.001
MIR-INF	316.88	12.1	309.15	17.5	0.010
MIR-NAS	320.60	13.6	309.67	19.1	0.001
MIR-TEM	304.44	9.1	296.44	17.2	0.004
MOR-AVG	292.25	13.0	282.92	14.5	0.001
MOR-SUP	291.69	13.8	283.17	14.6	0.003
MOR-INF	286.13	14.5	276.08	14.4	0.001
MOR-NAS	308.56	16.4	299.02	16.9	0.004
MOR-TEM	283.02	11.9	273.63	14.8	0.001

RNFL-AVG: Retinal nerve fiber thickness-Average;; GCC: Ganglion cell complex; CMT: Central macular thickness; MIR-AVG: Macular inner ring-Average; MIR-SUP: Macular inner ring -superior; MIR-INF: Macular inner ring -inferior; MIR-NAS: Macular inner ring -nasal, MIR-TEM: Macular inner ring -temporal; MOR-AVG: Macular outer ring -Average; MOR -SUP: Macular outer ring -superior; MOR -INF: Macular outer ring -inferior; MOR -NAS: Macular outer ring-nasal; MOR-TEM: Macular outer ring -temporal.

Table 2a. Correlations between the OCT measured variables in the ADHD Group

		AGE	RNFL-AVG	GCC-AVG	CMT	MIR-AVG	MIR-SUP	MIR-INF	MIR-NAS	MIR-TEM	MOR-AVG	MOR-SUP	MOR-INF	MOR-NAS
RNFL-AVG	R	-.12												
	P	0.567												
GCC-AVG	R	-.56*	.61*											
	P	.003	.0001											
CMT	R	-.35	.14	.41*										
	P	.079	.306	.003										
MIR-AVG	R	-.41*	.25	.67*	.75*									
	P	.036	.079	.0001	.0001									
MIR-SUP	R	-.38	.318*	.69*	.73*	.97*								
	P	.058	.022	.0001	.0001	.0001								
MIR-INF	R	-.39	.28	.69*	.70*	.98*	.96*							
	P	.050	.042	.0001	.0001	.0001	.0001							
MIR-NAS	R	-.30	.27	.58*	.77*	.96*	.94*	.93*						
	P	.136	.052	.0001	.0001	.0001	.0001	.0001						
MIR-TEM	R	-.52*	.05	.60*	.69*	.92*	.85*	.89*	.81*					
	P	.007	.675	.0001	.0001	.0001	.0001	.0001	.0001					
MOR-AVG	R	-.43*	.51*	.84*	.51*	.81*	.85*	.83*	.76*	.68*				
	P	.027	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001				
MOR-SUP	R	-.37	.53*	.79*	.49*	.72*	.78*	.75*	.69*	.57*	.95*			
	P	.061	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001			
MOR-INF	R	-.46*	.47*	.82*	.41*	.76*	.80*	.78*	.68*	.65*	.96*	.87*		
	P	.018	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001		
MOR-NAS	R	-.37	.45*	.76*	.53*	.81*	.83*	.83*	.78*	.68*	.95*	.88*	.88*	
	P	.058	.001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	
MOR-TEM	R	-.46*	.51*	.82*	.52*	.78*	.80*	.79*	.74*	.68*	.95*	.88*	.91*	.82*
	P	.018	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001

RNFL-AVG: Retinal nerve fiber thickness-Average;; GCC: Ganglion cell complex; CMT: Central macular thickness; MIR-AVG: Macular inner ring-Average; MIR-SUP: Macular inner ring -superior; MIR-INF: Macular inner ring -inferior; MIR-NAS: Macular inner ring -nasal, MIR-TEM: Macular inner ring -temporal; MOR-AVG: Macular outer ring -Average; MOR -SUP: Macular outer ring -superior; MOR -INF: Macular outer ring -inferior; MOR -NAS: Macular outer ring-nasal; MOR-TEM: Macular outer ring -temporal.

Table 2b. Correlations Between the OCT Measured Variables in the ADHD Group

		AGE	RNFL-AVG	GCC-AVG	CMT	MIR-AVG	MIR-SUP	MIR-INF	MIR-NAS	MIR-TEM	MOR-AVG	MOR-SUP	MOR-INF	MOR-NAS
RNFL-AVG	r	-.172												
	p	.400												
GCC-AVG	r	.012	.648**											
	p	.953	.000											
CMT	r	.070	.203	.354										
	p	.734	.321	.076										
MIR-AVG	r	-.071	.362	.466*	.448*									
	p	.732	.069	.017	.022									
MIR-SUP	r	.030	.285	.533**	.451*	.916**								
	p	.884	.159	.005	.021	.000								
MIR-INF	r	.004	.336	.400*	.267	.861**	.671**							
	p	.985	.093	.043	.188	.000	.000							
MIR-NAS	r	-.060	.337	.296	.294	.893**	.800**	.743**						
	p	.771	.092	.142	.144	.000	.000	.000						
MIR-TEM	r	.150	.141	.385	.468*	.866**	.842**	.748**	.639**					
	p	.465	.492	.052	.016	.000	.000	.000	.000					
MOR-AVG	r	-.089	.719**	.577**	.344	.561**	.601**	.479*	.487*	.455*				
	p	.664	.000	.002	.085	.003	.001	.013	.012	.020				
MOR-SUP	r	-.141	.618**	.551**	.366	.598**	.623**	.548**	.452*	.540**	.912**			
	p	.493	.001	.004	.066	.001	.001	.004	.020	.004	.000			
MOR-INF	r	-.035	.719**	.525**	.302	.473*	.471*	.459*	.467*	.331	.938**	.805**		
	p	.865	.000	.006	.134	.015	.015	.018	,016	.098	.000	.000		
MOR-NAS	r	-.102	.569**	.451*	.271	.657**	.704**	.541**	.650**	.446*	.864**	.769**	.755**	
	p	.621	.002	.021	.181	.000	.000	.004	.000	.023	.000	.000	.000	
MOR-TEM	r	-.089	.646**	.485*	.309	.440*	.447*	.377	.320	.483*	.848**	.757**	.829**	.597**
	p	.666	.000	.012	.124	.024	.022	.058	.111	.013	.000	.000	.000	.001

RNFL-AVG: Retinal nerve fiber thickness-Average;; GCC: Ganglion cell complex; CMT: Central macular thickness; MIR-AVG: Macular inner ring-Average; MIR-SUP: Macular inner ring -superior; MIR-INF: Macular inner ring -inferior; MIR-NAS: Macular inner ring -nasal, MIR-TEM: Macular inner ring -temporal; MOR-AVG: Macular outer ring -Average; MOR -SUP: Macular outer ring -superior; MOR -INF: Macular outer ring -inferior; MOR -NAS: Macular outer ring-nasal; MOR-TEM: Macular outer ring -temporal.

Table 3. Regression Analysis Models on the Independent Risk Factors for ADHD

Model 1								
	B	**S.E.**	**Wald**	**df**	**p**	**Odds Ratio**	**95% C.I.for EXP(B)**	
							Lower	**Upper**
AGE	-0.001	0.053	0	1	0.990	0.999	0.901	1.109
GENDER	1.965	1.195	2.704	1	0.100	7.135	0.686	74.226
RNFL-AVG	0.395	0.163	5.889	1	0.015	1.485	1.079	2.044
GCC-AVG	-0.023	0.131	0.032	1	0.859	0.977	0.755	1.264
CMT	-0.013	0.038	0.112	1	0.738	0.988	0.917	1.063
MIR-AVG	-1.891	2.222	0.724	1	0.395	0.151	0.002	11.756
MIR-SUP	0.564	0.616	0.836	1	0.361	1.757	0.525	5.881
MIR-INF	0.117	0.572	0.042	1	0.838	1.124	0.366	3.449
MIR-NAS	0.694	0.596	1.357	1	0.244	2.002	0.623	6.44
MIR-TEM	0.75	0.565	1.762	1	0.184	2.118	0.699	6.413
MOR-AVG	0.16	2.189	0.005	1	0.942	1.173	0.016	85.606
MOR-SUP	-0.191	0.522	0.134	1	0.715	0.826	0.297	2.3
MOR-INF	0.082	0.592	0.019	1	0.890	1.085	0.34	3.459
MOR-NAS	-0.106	0.555	0.036	1	0.849	0.9	0.303	2.669
MOR-TEM	-0.161	0.613	0.069	1	0.793	0.851	0.256	2.828
CONSTANT	-48.313	20.431	5.592	1	0.018	0		
Model 2								
RNFL-AVG	0.139	0.04	12.444	1	0.0001	1.15	1.064	1.242
MIR-AVG	1.13	0.5	5.24	1.0	0.022	3.09	1.18	8.13
MIR-SUP	0.094	0.078	1.452	1	0.037	1.099	1.003	1.282
MIR-NAS	0.18	0.079	5.197	1	0.023	1.198	1.026	1.399
MIR-TEM	0.211	0.079	7.099	1	0.008	1.235	1.057	1.442
CONSTANT	-24.613	6.703	13.483	1	0.0001	0		

RNFL-AVG: Retinal nerve fiber thickness-Average;; GCC: Ganglion cell complex; CMT: Central macular thickness; MIR-AVG: Macular inner ring-Average; MIR-SUP: Macular inner ring -superior; MIR-INF: Macular inner ring -inferior; MIR-NAS: Macular inner ring -nasal, MIR-TEM: Macular inner ring -temporal; MOR-AVG: Macular outer ring -Average; MOR -SUP: Macular outer ring -superior; MOR -INF: Macular outer ring -inferior; MOR -NAS: Macular outer ring-nasal; MOR-TEM: Macular outer ring -temporal.

are highly correlated with each according to their significance level. All parameters were added to the regression analysis for Model 1 (Table 3). In Model 2, the real independent risk factors for ADHD obtained by the Backward-Wald method corresponded to the OCT measurements of RNFL-AVG, MIR-AVG, MIR-SUP, MIR-NAS and MIR-TEM (Table 3). These results indicate that having ADHD is 1.15 (95% CI 1.1-1.2) times more likely with low RNFL-AVG levels; 1.1 (95% CI 1.0-1.3) times more likely with low MIR-SUP levels; 1.2 (95% CI 1.0-1.4) times more likely with low MIR-NAS levels; 1.2 (95% CI 1.1-1.4) times more likely with low MIR-TEM levels and 3.1 (95% CI 1.2-8.1) times more likely with low MIR-AVG levels (Table 3).

DISCUSSION

In this study, we found a significant decrease in retinal nerve fiber thickness, ganglion cell complex, central macular thickness, mean thickness of the inner and outer macular rings, and the thicknesses measured separately in the four quadrants in the adult ADHD group as compared to the control group.

To the best of our knowledge, our study is the first to investigate the retina with OCT in adult ADHD cases. There are a few studies on this subject in paediatric ADHD cases. The RNLF thinness measured by Hergüner et al. (2016) in the nasal quadrant of children with ADHD was lower as compared to the controls, which is consistent with our results, although their macular thickness measurements of the two groups did not differ signficiantly.

In another recent study comparing 12 ADHD patients and 13 healthy controls on macular thickness measured by OCT and also on the CNS cortical thicknesses measured by cranial MRI, an increase in macular thickness was found in the ADHD cases, but the average cortical thicknesses of the groups did not differ significantly, although an insignificant thickening of the parietal cortex was observed in the ADHD group (Bae et al. 2019). However, other studies have reported decreased cortical thickness, most prominently in the prefrontal region and the precentral gyrus in the brains of children with ADHD (Cortese and Castellanos 2012, Narr et al. 2009). The reported increase in macular thickness may be due to the lack of difference in the cortical thickness of the ADHD and the control groups.

Neuropsychiatric studies have reported that retinal layer thinning predicts cortical atrophy (London et al. 2013). Also, the significant reduction in cortical thickness was shown to be associated with symptom persistence in adult ADHD (Shaw et al. 2013). Considering that persistent symptoms continue to adulthood in approximately 50% of the children diagnosed with ADHD (Faraone et al. 2015), there may be some differences between the adult ADHD cases with long term exposure to persistent symptoms and the paediatric ADHD cases. As the differentiation of paediatric ADHD cases that will clinically improve from the cases that will reflect the sysmptoms to adulthood has not yet been possible, the results of the studies conducted with paediatric cases can be expected to vary. Given the neurodevelopmental nature of ADHD, some retinal involvement can be expected in childhood. Indeed, comparison of RNFL thickness, ganglion cell layer (GCL) and optic nerve thickness in paediatric ADHD and control groups indicated significantly lower GCL and optic nerve thickness in the ADHD group(Bodur at al. 2018). Since our ADHD participants were adults, our results may indicate symptom persistence and chronicity in ADHD.

Retinal changes have been reported to correlate with disease duration and persistence in many psychiatric disorders (Ascaso et al. 2015, Lee et al. 2013, Mehraban et al. 2016). However, changes due to disease progress should also be distinguished from age-related retinal changes in the normal population. Although the effect of aging on the ganglion cell complex (GCC) is clinically small, being reported as 1.59 μm in decades of increasing age, it was stressed that age-related changes should be considered (Kim et al. 2011).

When we evaluated the group OCT measurement data of our study; we found that GCC-AVG, MIR-AVG, MIR-SUP, MIR-TEM, MOR-AVG, MOR-INF and MOR-TEM measurements decreased significantly with age in the ADHD group, without a similar negative correlation between age and retinal measurements in the control group. Age was not found to be a statistically significant independent risk factor for ADHD in many tested statistical models. The regression analysis carried out in this study showed the independent risk factors for ADHD to be the RNFL-AVG, MIR-AVG, MIR-SUP, MIR-NAS and MIR-TEM measurements. In our study the median age of the ADHD and control groups were close (33.58 and 32.69 years, respectively), such that the age related decrease in RNLF values (Ryoo et al. 2018) were being observed in groups of very young ages. Therefore, we can say that our results are an indicator of disease-related axonal damage rather than aging per se. It has been shown that RNFL thickness in Parkinson's disease can predict axonal damage, and that disease duration affects the RNFL, ganglion cell layer and inner plexiform layer thicknesses (Garcia-Martin et al. 2014).

Our results show thinning in the average thickness of the retinal nerve fibers, reduction in the mean thickness of the macular inner ring and the nasal, superior and temporal quadrants of the macular inner ring to be independent risk factors for ADHD. We could not find a study in the literature to compare our results on the basis of RNFL and macular volume reduction in adult ADHD. However, similarly to our results, thinning of the central macula and macular inner temporal, nasal and inferior regions were reported in patients with bipolar disorder (Polo et al. 2019). Macular inner ring thickness and macular volume decrease in schizophrenia patients without an incidence of psychotic attack in the previous 6 months, and also pronounced RNFL thinning and macular volume decrease in the chronic phase of schizophrenia have been reported (Ascaso et al. 2015, Lee et al. 2013).

It is difficult to explain which retinal layer is more affected in any disease and the underlying causality, but since the macula contains fewer different anatomical structures such as large retinal blood vessels, it is at a more convenient location than the peripapillary retina for ruling out any masking conditions affecting RNFL measurement and seeing any damage to retinal ganglion cells at an early stage. Also, the retinal ganglion cells are most densely located in the macula, forming a multicellular layer. Therefore, loss of axons in the macular rings causes thinning of the retinal ganglion cell layer (Kardon 2011). The macular involvement in our study seems to be an indicator of axonal loss probably resulting from the chronicity of the disease.

The thalamus is an important center receiving strong dopaminergic projections and with connections to the cerebral cortex, striatum, and the cerebellum which modulate a series of cognitive areas (Dorph-Petersen and Lewis 2017, van Heeringen at al. 2011). Electroencephalographic studies show that the impulse traffic through the thalamus is abnormal in ADHD patients (Rowe et al. 2005a). Thalamic hypoactivation has been determined and other abnormalities have been reported in ADHD (Cortese at al. 2012). Considering that ADHD is a disorder with imbalances in different neurotransmitters and neural networks (Rowe at al. 2005b), central neurotransmitter imbalances in ADHD may cause damage to the retinal layers by acting through the thalamo-cortical projection system and cortical networks. One possible mechanism that may explain these changes in the retina is the retrograde transynaptic degeneration (RTSD) theory, which proposes that cell loss occurs in the ganglion cells and retinal nerve fibers secondarily to synaptic dysfunction in the thalamus that has attachments to the optic nerve fibers, and resulting in atrophy of the inner retinal layers with the downward reflection of the axonal damage in the upper visual system (Dinkin 2017).

Hence, we can assume that our results reflect synaptic loss and neuronal atrophy. Our findings support the reflection of brain pathologies on the retina by showing that there are retinal changes in adult ADHD, although retinal findings are not specific to ADHD. Being the first controlled investigation on the subject in adult patients make up the strengths of our study, while having been cross sectional and carried out in a single center with a small number of participants are its limitations. Although the results are based on a cross sectional study, we believe that OCT measurements can be used as potential biomarkers to determine the persistence of the disease which should be further investigated by appropriately reinforced longitudinal studies in the future..

CONCLUSION

This study is the first to report the relationship between retinal changes and adult ADHD with results demonstrating the thinning of the retinal layers in ADHD patients. OCT measurements can be used to identify the biomarkers of clinically sigfnificant structural changes in the retina in ADHD. Thus, OCT can be a diagnostic tool for monitoring the course and prognosis of pediatric ADHD cases, determining the extent to which ADHD will reflect on adulthood and discriminating adult ADHD patients from healthy controls. However, next to the comparison of adult ADHD and control groups, many follow-up studies are needed in paediatric ADHD cases.

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