Original Article

Relationship between autism spectrum disorder and peripapillary intraretinal layer thickness: a pediatric retrospective cross-sectional study

Yuexuan Wang[1#], Zhaoqi Zhu[2#], Yonglu Wang[3], Mingchao Li[1,4], Xiao Ma[1], Kun Huang[1], Huiyun Gao[3], Youqiang Zhang[5], Qiang Chen[1], Weiwei Zhang[2], Xiaoyan Ke[3]

[1]School of Computer Science and Engineering, Nanjing University of Science and Technology, Nanjing, China; [2]Department of Ophthalmology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [3]Child Mental Health Research Center, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China; [4]Future Lab, Tsinghua University, Beijing, China; [5]School of Internet of Things, Nanjing University of Posts and Telecommunications, Nanjing, China

Contributions: (I) Conception and design: Yuexuan Wang, M Li, Q Chen, W Zhang, X Ke; (II) Administrative support: X Ma, K Huang, Q Chen, W Zhang, X Ke, Y Zhang; (III) Provision of study materials or patients: Z Zhu, W Zhang, Yonglu Wang, H Gao, X Ke; (IV) Collection and assembly of data: Yuexuan Wang, Z Zhu, Yonglu Wang, H Gao; (V) Data analysis and interpretation: Yuexuan Wang, Z Zhu, Yonglu Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Qiang Chen, PhD. School of Computer Science and Engineering, Nanjing University of Science and Technology, No. 200 Xiaolingwei Street, Xuanwu District, Nanjing 210094, China. Email: chen2qiang@njust.edu.cn; Weiwei Zhang, PhD. Department of Ophthalmology, The First Affiliated Hospital of Nanjing Medical University, No. 300 Guangzhou Road, Gulou District, Nanjing 210029, China. Email: zhang_weiwei@139.com; Xiaoyan Ke, PhD. Child Mental Health Research Center, The Affiliated Brain Hospital of Nanjing Medical University, No. 264 Guangzhou Road, Gulou District, Nanjing 210029, China. Email: kexiaoyan@njmu.edu.cn.

Background: Autism spectrum disorder (ASD) often presents with atypical visual processing, prompting investigation into its connection with retinal features. This study aimed to (I) compare intraretinal layer thickness in the peripapillary region between ASD and neurotypical (NT) groups, (II) assess associations between intraretinal layer thickness and clinical parameters (social functioning and cognitive levels) in ASD subjects, and (III) evaluate the potential of intraretinal layer thickness as a biomarker for ASD.

Methods: Participants were recruited through convenience sampling from the Children's Mental Health Research Center at The Affiliated Brain Hospital of Nanjing Medical University and the Department of Ophthalmology at The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, between December 2019 and August 2023. Intraretinal layer thickness in peripapillary region was quantified using optic coherence tomography images with automated layer segmentation performed by OCTExplorer software on 47 individuals with ASD (aged 7–13 years) and age- and sex-matched NT controls. Inter-group comparisons were conducted using unpaired *t*-tests, Welch's *t*-tests, or Mann-Whitney U tests as appropriate. Correlations with social functioning (measured by Social Responsiveness Scale scores) and cognitive levels [measured by total intelligence quotient (IQ) scores] were examined using the Spearman correlation coefficient. Stepwise regression analysis was conducted to assess predictive power.

Results: Significant inter-group differences (P<0.05) were observed in ganglion cell layer and inner nuclear layer (INL) thickness across global and specific quadrant regions. Participants had a mean age of 9.57±1.83 years in the ASD group and 9.89±1.70 years in the age-matched NT group. While no correlation was found between retinal sublayer thickness and social functioning on ASD subjects (all P>0.05), there was a notable correlation between INL thickness in the infero-nasal quadrant and cognitive level (r=0.381, P=0.014). Stepwise regression analysis identified global INL thickness as a significant predictor of total IQ

scores (β=3.986, P=0.034), with an R^2 of 0.110 and a root mean square error of 21.900.

Conclusions: This study highlights significant differences in retinal features between ASD and NT groups, with implications for understanding ASD pathogenesis and complexity. The findings suggest that easily observable retinal features hold promise as biomarkers for ASD, warranting further investigation.

Keywords: Autism spectrum disorder (ASD); retinal features; intraretinal layer thickness; optic coherence tomography (OCT); biomarker

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Introduction

Autism spectrum disorder (ASD) is a profound neurodevelopmental condition characterized by enduring deficits in social communication and interaction, coupled with restricted, repetitive patterns of behavior, interests, or activities (1). The global prevalence of ASD has reached 1% and exhibits a persistent upward trajectory (2-4). The retina, serving as an extension of the central nervous system (CNS), shares structural and functional parallels with the brain. Specifically, the retinal plexiform and nerve fiber layers bear semblance to the white matter, while the nuclear and ganglion cell layers resemble the cerebral gray matter (GM) (5). Neurophysiologically, the retina and brain predominantly consist of neurons and glial cells, exhibiting akin interconnections among glial cells (6,7). Furthermore, the receptors for the main neurotransmitters of both the retina and brain are nearly identical (8,9). The retina and brain also share similar mechanisms in neuroimmune defence and response (10,11). In addition, both the retina and the brain necessitate analogous blood supply owing to comparable angiogenesis (12). The inner blood-retina barrier mirrors the structure, function, and mechanism of the blood-brain barrier (10,13). These shared characteristics position the retina as a promising avenue for ASD exploration.

As the starting point of the visual system, the retina is susceptible to changes of the body. Individuals with ASD commonly face challenges, manifesting as hypersensitivity or insensitivity to visual stimuli and reduced attention to social gaze and facial expressions (14-17). Previous electroretinogram (ERG) studies on ASD individuals have reported functional retinal changes in ASD (18,19). And a recent ERG-based research holds that sensory processing differences in ASD individuals are upstream of more complex autistic traits and potential intervention targets and report that the autistic retina displays hyper-responsive reaction to single white flashes, indicating altered retinal sensitivity in ASD individuals (20). These findings suggest that differences in retinal dynamics may correlate with the severity of autistic traits. Moreover, early visual abnormalities may significantly impact learning processes and contribute to the social and communicative development of infants (21). Therefore, the retina exploration in the context of ASD biomarker holds potential and may provide additional insights into ASD. This paper focuses on retinal structure changes near the optic disc, which serves as the gateway of the optic nerve to the brain and the inlet of the primary blood supply to the retina.

The unique advantage of the retina over other CNS structures lies in its direct observability and the retinal neurons are unmyelinated unlike the brain. While traditional imaging modalities, such as color fundus photographs and fundus fluorescein angiography, have been pivotal in ophthalmology, their two-dimensional (2D) limitations and potential adverse reactions due to dyes are still salient. Optical coherence tomography (OCT), utilizing low-coherence light, offers non-invasive, three-dimensional (3D) imaging with micro-scale resolution, emerging as a powerful tool for diagnosing, observing, and quantifying retinal diseases (22-24). In light of these advancements, our study utilizes OCT to investigate the relationship between intraretinal layer thickness and ASD.

To the best of our knowledge, only a limited number of studies have focused on alterations near the optic disc in autism (25-30). These studies have predominantly explored the peripapillary retinal nerve fiber layer (pRNFL), without sufficiently investigating other intraretinal layers. Additionally, as the study of retinal changes in autism is an emerging field, previous studies have exhibited considerable variability in sample sizes and age distributions and have not

reached consistent results. Revisiting previous studies with a larger sample size, this study seeks to clarify the relationship between intraretinal layer thickness and ASD.

Notably, OCT imaging devices are primarily crafted for the examination of retinal diseases, prioritizing pRNFL measurements in optic disc related region due to their intimate connection with ocular conditions. This emphasis resulted in a predominant focus on RNFL in previous ASD studies conducted in this region. However, as the pathological mechanisms underlying ASD remain unclear, the exclusive association of observed changes with RNFL alterations remains uncertain. Therefore, it is imperative to comprehensively investigate all retinal sublayers within the peripapillary region. This study aims to conduct thorough global and quadrantal thickness analyses of all intraretinal layers within the peripapillary region, incorporating clinical parameters related to social functioning and cognitive level in exploratory experiments. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-753/rc).

Methods

Participants

This cross-sectional study received approval from the Medical Ethics Committee of Nanjing Medical University (Approval ID: 2020-SR-363) and adhered to the principles of the Declaration of Helsinki (as revised in 2013). Recruitment transpired from December 2019 to August 2023 and encompassed both an ASD group and a neurotypical (NT) control group. ASD participants were sourced from the Specific Disease Cohort of ASD in the Children's Mental Health Research Center, Nanjing Brain Hospital/The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China, while NT subjects were recruited from the local communities through the Department of Ophthalmology, Jiangsu Province Hospital/The First Affiliated Hospital of Nanjing Medical University, Nanjing, China. Informed consent was obtained from the participants' parents or guardians. The enrollment process of participants is shown in *Figure 1*.

Inclusion criteria for the ASD group comprised: (I) a confirmed diagnosis of ASD based on DSM-5 (1) criteria was made by two deputy chief physicians or above in the Department of Child and Adolescent Psychiatry of Nanjing Brain Hospital; (II) age ranging from 7 to 13 years; (III) full-scale intelligence quotient (IQ) of Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (31) measurement ≥70; (IV) right-handedness; (V) the child and their parent/guardian agreed to participate in this study. Exclusion criteria for the ASD group included: (I) identifiable causes of autism; (II) intellectual development disorder or other mental diseases ; (III) a clear history of neurological diseases, traumatic brain injury, or serious physical diseases; (IV) a history of any psychotropic drugs in the past 3 months; (V) signs or history of eye disorders, including a refractive error exceeding 3 spherical diopters, amblyopia, and strabismus; (VI) difficulties in cooperating for obtaining high-quality OCT images without artifacts; and (VII) OCT signal strength below 6.

Inclusion criteria for the NT group comprised: (I) age ranging from 7 to 13 years; (II) the child and their parent/guardian agreed to participate in this study. Exclusion criteria for the NT group included: (I) the inability to rule out ASD based on Strengths and Difficulties Questionnaire (32); (II) a clear history of neurological diseases, traumatic brain injury, or serious physical diseases; (III) signs or history of eye disorders, including a refractive error exceeding 3 spherical diopters, amblyopia, and strabismus; (IV) difficulties in cooperating for obtaining high-quality OCT images without artifacts; and (V) OCT signal strength below 6.

All participants underwent a comprehensive ophthalmic examination, including autorefraction, intraocular pressure (IOP) measurement, slit lamp biomicroscopy, mydriasis funduscopy, OCT, conducted by experienced ophthalmologists. ASD participants underwent additional clinical psychological evaluations performed by professionally trained psychologists or psychiatrists in the Child Psychology Research Center of Nanjing Brain Hospital utilizing: (I) Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (33,34); (II) Autism Diagnoses Interview-Revised (ADI-R) (34,35); (III) the Chinese version of Social Responsiveness Scale (SRS) (36,37); and (IV) the Chinese version of WISC-IV (31).

OCT image acquisition and feature extraction

In this study, OCT images were acquired using a commercial 70-kHz SD-OCT system (RTVue XR Avanti, Optovue Inc., CA, USA) with a center wavelength of 840 nm, an acquisition rate of 70,000 A-scans per second, an axial resolution of 5 μm in tissue, and a lateral resolution of 11.25 μm. An OCT image centered on the disc with a field of

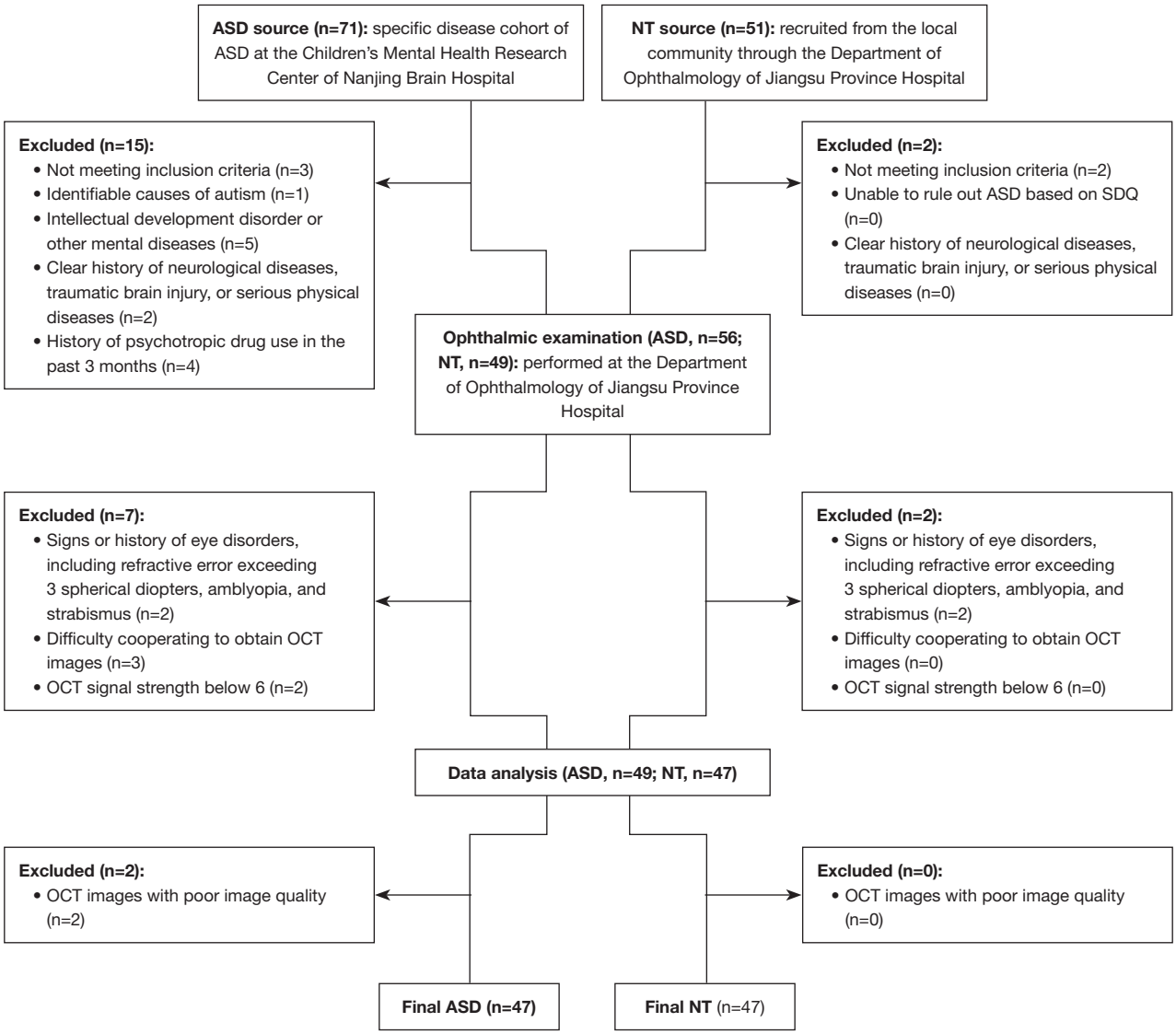

Figure 1 Flow diagram of the enrollment process of patients. ASD, autism spectrum disorder; NT, neurotypical; SDQ, Strengths and Difficulties Questionnaire; OCT, optic coherence tomography.

view of 4.5×4.5 mm and a depth of approximately 1.92 mm was scanned. Each 3D OCT volume consisted of 400 B-scans, each of which included 400 A-scans with 640 pixels per A-scan, and each fixed location was scanned at least twice to ensure high-quality images (*Figure 2A*). Intraretinal layer thickness analysis encompassed different regions, including the global peripapillary region and 6 quadrantal subregions (*Figure 2B*): supero-temporal, supero-nasal, nasal, infero-nasal, infero-temporal, and temporal quadrants (ST, SN, N, IN, IT, and T). Intraretinal layer borders were automatically calculated by OCTExplorer software (v.3.8.0; The Iowa Institute for Biomedical Imaging, Iowa, USA) (38-40) and were utilized to measure the thickness of 10 retinal sublayers (*Figure 2C*) including the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), Henle fiber layer/outer nuclear layer/myoid zone (HOAM), ellipsoid zone (EZ), outer segment (OS), outer segment PR/RPE complex and subretinal virtual space (OPRS), and retinal pigment epithelium (RPE).

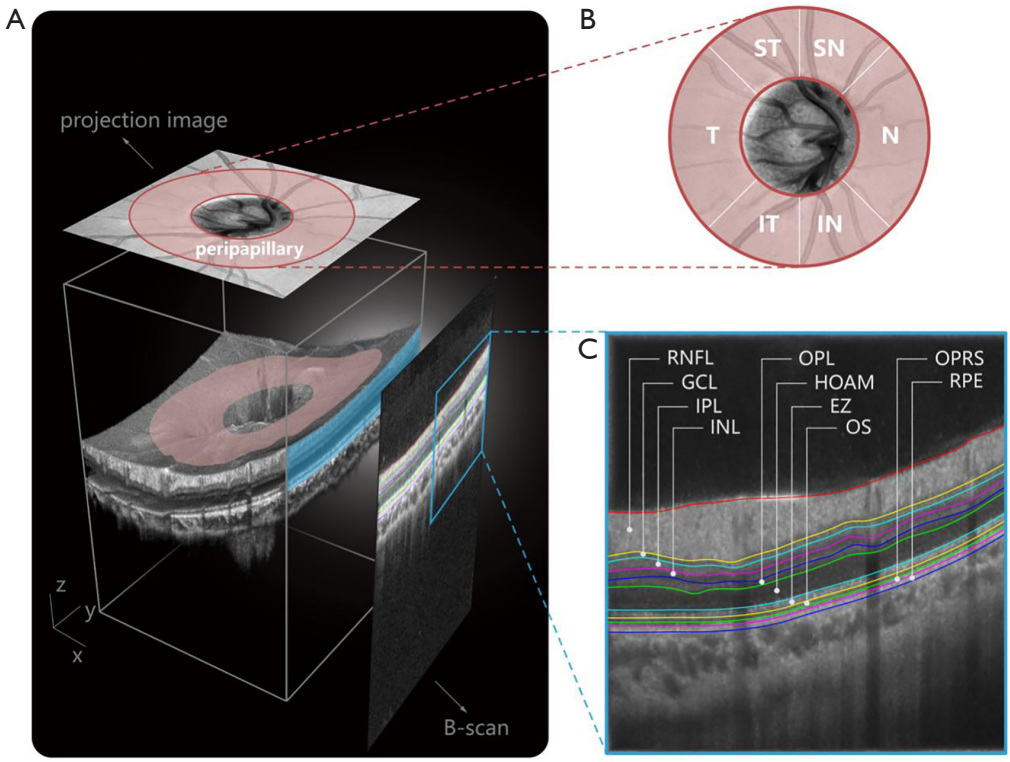

Figure 2 Schematic representation of OCT region segmentation for statistical analysis. (A) Illustration of an OCT volumetric data. (B) Quadrant segmentation. (C) Layer segmentation. ST, supero-temporal quadrant; SN, supero-nasal quadrant; N, nasal quadrant; IN, infero-nasal quadrant; IT, infero-temporal quadrant; T, temporal quadrant; RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform; HOAM, Henle fiber layer/outer nuclear layer/myoid zone; EZ, ellipsoid zone; OS, outer segment; OPRS, outer segment PR/RPE complex and subretinal virtual space; RPE, retinal pigment epithelium; OCT, optic coherence tomography.

Statistical analysis

Statistical analysis was conducted using MATLAB (MathWorks, 2021). If data from both eyes of participants were available, the final parameters were averaged bilaterally. Otherwise, parameters from the included single eye were used. Data distribution was presented as the mean ± standard deviation (SD). The Shapiro-Wilk test was employed to assess the normality of values, while the two-sample F-test gauged homogeneity of variances. The unpaired *t*-test and Welch's *t*-test were utilized for comparisons between continuous variables that satisfied normal distribution and those that only partially met the normal distribution, respectively. The Mann-Whitney U test was employed for comparisons where at least one group did not meet the normal distribution. The Chi-squared test was applied for non-continuous variables. Correlations between clinical parameters (total SRS scores and total IQ scores) and intraretinal layer thickness were determined using the Spearman correlation coefficient. A significance level of $P<0.05$ was considered statistically significant for the two-tailed test. Stepwise regression was employed to identify specific intraretinal layers that significantly contribute to the prediction of ASD clinical parameters. The thresholds selected were entry significance level less than 0.05 and removal significance level greater than 0.1.

Results

Participants

A total of 177 eyes from 94 participants were included in this study, including 47 ASD subjects (41 boys and 6 girls) and 47 age- and sex-matched NT subjects (mean age: 9.57±1.83 *vs.* 9.89±1.70 years). Twenty-three SRS scales of children with ASD were excluded due to parents' irregular

Table 1 Demographics and clinical parameters

Parameter	ASD (n=47)	NT (n=47)	P
Sex (male/female)	41/6	41/6	1.000[a]
Age (years)	9.57±1.83	9.89±1.70	0.157[b]
Laterality			0.936[a]
Left eye	42	47	
Right eye	41	47	
IQ	98.34±22.91; NA =6	–	–
ADI-(SI+CO)	30.10±4.60	–	–
ADI-Total	37.49±4.98	–	–
ADOS-(S+C)	13.34±4.45	–	–
ADOS-Total	16.07±5.58	–	–
SRS-Aw	16.38±2.95; NA =23	–	–
SRS-Cog	29.33±7.94; NA =23	–	–
SRS-Com	46.17±10.40; NA =23	–	–
SRS-Mo	21.29±4.16; NA =23	–	–
SRS-Ma	24.75±7.75; NA =23	–	–
SRS-Total	137.83±29.70; NA =23	–	–

Data are presented as mean ± standard deviation or n. [a], χ^2 test for categorical variables; [b], Mann-Whitney U test. NA indicates the number of unavailable data points. ASD, autism spectrum disorder; NT, neurotypical; IQ, score of full-scale intelligence quotient of the Chinese version of Wechsler Intelligence Scale for Children, Fourth Edition; ADI-(SI+CO), total score of Social Interaction and Communication Module in the Autism Diagnostic Interview-Revised; ADI-Total, total score of the Autism Diagnostic Interview-Revised; ADOS-(S+C), total score of combined social-communication domain in ADOS; ADOS-Total, total score of ADOS; ADOS, Autism Diagnostic Observation Schedule, Second Edition; SRS-Aw, score of the social awareness domain in SRS; SRS-Cog, score of social cognition domain in SRS; SRS-Com, score of social communication domain in SRS; SRS-Mo, score of social motivation domain in SRS; SRS-Ma, score of Autistic Mannerisms domain in SRS; SRS-Total, total score of SRS; SRS, Social Responsiveness Scale.

completion or completion by non-primary caregivers. Six children with ASD were uncooperative to give valid IQ and were excluded from IQ related statistics. Due to poor cooperation, 5 left eyes and 6 right eyes were excluded from the ASD group. *Table 1* gives the demographics and clinical characteristics of included samples.

Intraretinal layer thickness differences between ASD and NT

Global thickness statistical analysis revealed that the thickness of GCL and INL in the ASD group was significantly higher compared to the control group (P=0.022 and P<0.001). Further quadrant analysis showed significant differences in the thickness of the IN, IT, and T quadrants of the GCL layer, as well as the N, IN, IT, and T quadrants of the INL layer, between the ASD and NT groups, with greater thickness observed in the ASD group as shown in *Table 2*.

Correlation between intraretinal thickness and clinical parameters

For the thickness of the GCL and INL, which showed intergroup differences, further analysis was conducted to explore their correlation with the social functioning quantified by SRS scale and cognitive level quantified by IQ based on WISC-IV. According to Spearman's correlation analyses, there were no significant correlations observed between the subscale and total SRS scores and the thickness of the involved intraretinal layers or their respective sub-quadrants as shown in *Table 3*. The thickness from IN

Table 2 Arithmetic mean of the global and quadrantal peripapillary intraretinal layer thickness and results of statistical difference (μm)

Layer	ASD	NT	P
RNFL	130.53±16.36	127.11±13.43	0.106[a]
GCL*	14.15±1.30	13.71±1.67	0.022[a]
ST	11.86±2.23	11.68±2.01	0.700[c]
SN	12.89±2.83	12.73±2.62	0.774[c]
N	14.79±2.23	14.83±2.84	0.283[a]
IN*	12.48±1.76	11.86±2.11	0.035[a]
IT*	11.58±2.41	10.55±1.62	0.030[a]
T*	17.41±1.97	16.69±2.44	0.018[a]
IPL	29.23±1.51	28.96±1.22	0.360[c]
INL*	16.69±1.88	15.59±1.88	<0.001[a,**]
ST	15.10±2.79	14.35±1.74	0.128[b]
SN	14.59±2.44	14.13±3.01	0.159[a]
N*	16.63±2.60	15.72±2.86	0.037[a]
IN*	15.06±2.88	13.84±2.40	0.006[a]
IT*	14.85±2.69	13.44±2.02	0.006[c]
T*	20.33±3.00	18.86±2.88	0.019[c]
OPL	25.26±1.21	24.95±1.18	0.215[c]
HOAM	59.06±4.75	60.26±7.45	0.344[a]
EZ	14.38±1.60	13.94±1.42	0.162[c]
OS	9.42±1.50	9.53±1.47	0.716[c]
OPRS	11.81±3.48	11.74±2.27	0.917[b]
RPE	20.53±0.94	20.52±0.55	0.211[a]

Data are presented as mean ± standard deviation. [a], Mann-Whitney U test; [b], Welch's *t*-test; [c], Student's *t*-test. *, significant differences; **, significant results after Bonferroni correction. ASD, autism spectrum disorder; NT, neurotypical; RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; ST, supero-temporal quadrant; SN, supero-nasal quadrant; N, nasal quadrant; IN, infero-nasal quadrant; IT, infero-temporal quadrant; T, temporal quadrant; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform; HOAM, Henle fiber layer/outer nuclear layer/myoid zone; EZ, ellipsoid zone; OS, outer segment; OPRS, outer segment PR/RPE complex and subretinal virtual space; PR, photoreceptor; RPE, retinal pigment epithelium.

quadrant of INL showed significant correlation with IQ (r=0.381, P=0.014) as shown in *Table 4*.

Predictive potential of intraretinal thickness for ASD

Based on the results of the stepwise regression analysis, our aim was to determine which retinal layer thickness have the potential for effective prediction of social functioning (subscale and total SRS scores) and cognitive level (total IQ score) in individuals with ASD. With regard to the total SRS score, it was not possible to identify any specific retinal sublayer thickness that demonstrated effective predictive performance. However, in the case of the total IQ score, a significant positive correlation was observed between the global thickness of INL and the total IQ score as shown in *Table 5*. Although the overall R^2 is not at a high level, this association exhibits statistical significance.

Discussion

The retina serves as the site for photoelectric conversion and intricately regulates various enzymes and proteins.

Table 3 Correlation of autistic social functioning quantified by subscale and total SRS scores against intraretinal layer thickness with inter-group differences

Layer thickness	SRS-Aw		SRS-Cog		SRS-Com		SRS-Mo		SRS-Ma		SRS-Total	
	r	P	r	P	r	P	r	P	r	P	r	P
GCL	0.018	0.935	−0.116	0.591	−0.156	0.467	−0.273	0.197	−0.149	0.488	−0.128	0.551
IN	−0.222	0.297	−0.079	0.712	−0.209	0.328	0.006	0.977	−0.119	0.580	−0.119	0.579
IT	−0.045	0.834	−0.008	0.969	0.019	0.931	−0.257	0.225	−0.033	0.878	0.005	0.981
T	−0.060	0.782	−0.051	0.814	−0.157	0.463	−0.123	0.568	−0.096	0.657	−0.045	0.834
INL	−0.203	0.342	−0.112	0.604	−0.281	0.183	−0.189	0.376	−0.236	0.266	−0.156	0.467
N	−0.209	0.328	−0.321	0.126	−0.336	0.108	0.128	0.551	−0.334	0.111	−0.248	0.243
IN	−0.439	0.032	−0.057	0.793	−0.189	0.377	0.034	0.874	−0.174	0.417	−0.098	0.649
IT	0.017	0.937	−0.007	0.973	−0.186	0.383	−0.325	0.122	−0.149	0.487	−0.092	0.668
T	0.011	0.961	−0.080	0.711	−0.292	0.166	−0.387	0.061	−0.232	0.274	−0.150	0.484

SRS, the Chinese version of Social Responsiveness Scale; SRS-Aw, score of the social awareness domain in SRS; SRS-Cog, score of social cognition domain in SRS; SRS-Com, score of social communication domain in SRS; SRS-Mo, score of social motivation domain in SRS; SRS-Ma, score of Autistic Mannerisms domain in SRS; SRS-Total, total score of SRS; GCL, ganglion cell layer; IN, infero-nasal quadrant; IT, infero-temporal quadrant; T, temporal quadrant; INL, inner nuclear layer; N, nasal quadrant.

Table 4 Correlation of autistic cognitive level quantified by score of full-scale intelligence quotient of WISC-IV against thickness of retinal layers with inter-group differences

Layer thickness	IQ	
	r	P
GCL	−0.167	0.297
IN	0.093	0.564
IT	−0.083	0.605
T	−0.243	0.125
INL	0.035	0.828
N	0.270	0.088
IN*	0.381	0.014
IT	−0.095	0.555
T	−0.153	0.340

*, significant differences. WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; IQ, score of full-scale intelligence quotient of WISC-IV; GCL, ganglion cell layer; IN, infero-nasal quadrant; IT, infero-temporal quadrant; T, temporal quadrant; INL, inner nuclear layer; N, nasal quadrant.

Consequently, it is highly susceptible to systemic changes and may act as an indicator for various diseases (17), offering a potential avenue for aiding in the diagnosis and understanding of the pathological mechanisms of ASD. This study substantiates this notion by revealing that, compared to the control group, individuals with ASD manifested thickening of the GCL and INL within the peripapillary global region and its quadrants. Additionally, we explored the relationship between the global and quadrant-specific thickness of GCL and INL and the social functioning (i.e., total SRS score) or cognitive level (i.e., total IQ score) of ASD children, exposing a significant correlation between the inferior-nasal INL thickness and IQ, and no statistically significant correlation between the selected thickness and SRS. Furthermore, we employed stepwise regression to discern the most influential predictors within the complex interplay of retinal features and clinical outcomes, finding that the global INL thickness fit well with IQ. However, none of the layer thicknesses demonstrated predictive capability for the SRS parameter. To the best of our knowledge, this study represents the first comprehensive exploration of all intraretinal layers within the peripapillary region of children with ASD.

Research gaps in assessing retinal changes in ASD

Despite the retina's potential for ASD research, only a few studies employing OCT have explored retinal alterations associated with autism, with a predominant focus on the pRNFL in the investigations related to the retinal disc area. Emberti Gialloreti *et al.* (25) conducted a study

Table 5 Stepwise regression of intraretinal layer thickness on IQ in ASD group

Step	Model	β	SE	t	P	RMSE	R^2	Adjusted R^2
1	(Intercept)	31.613	30.620	1.032	0.308			
	INL	3.986	1.818	2.193	0.034	21.900	0.110	0.087

β indicates the regression coefficient. IQ, score of full-scale intelligence quotient of WISC-IV; ASD, autism spectrum disorder; SE, standard error; RMSE, root mean square error; INL, the thickness of the inner nuclear layer; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition.

comparing the pRNFL thickness in 24 individuals with ASD and 24 NT young adults (mean age: 23.4±6.0 years). Their findings revealed a thinning of the pRNFL in the nasal quadrant among the ASD group and established a negative correlation between pRNFL thickness in ASD individuals and verbal IQ. In contrast, García-Medina *et al.* (26) investigated pRNFL thickness in 27 ASD individuals (mean age: 13.7±3.0 years) compared to 27 NT controls, reporting a thickening in the temporal inferior, nasal inferior, and inferior quadrants of pRNFL in the ASD group. They further identified a positive correlation between pRNFL thickness in the temporal-inferior region of ASD individuals and both verbal and nonverbal IQ. However, a subsequent study by Garcia-Medina *et al.* (27) found no significant differences in pRNFL thickness between 13 ASD and 14 NT individuals (mean age: 16.6±3.0 years). Bozkurt *et al.* (28) extended the investigation to 40 ASD individuals and 40 control individuals (mean age: 9.4±1.6 years), discovering significantly lower pRNFL thickness in the temporal, temporal superior, nasal superior, temporal inferior, and global regions in ASD individuals, with no observed correlation between pRNFL thickness and the severity of ASD symptoms. Friedel *et al.* (29) conducted a comparative study involving 34 ASD individuals and 31 NT controls (mean age: 35±10 years) but did not observe any changes in pRNFL thickness in individuals with ASD. In a more recent study by Bağcı *et al.* (30) encompassing 41 ASD subjects, 38 healthy siblings, and 43 healthy controls (average age: 12, 13, and 12 years, with a range of age: 5–18, 4–18, and 7–17 years), no significant differences were found in pRNFL thickness among these groups.

In light of these varying findings, the assessment of intraretinal layer changes in individuals with ASD presently lacks a consensus. Firstly, retinal imaging in ASD is a relative new field, with ongoing studies yet to attain a sufficient scale of sample size. Secondly, the age distribution among participants in relevant studies exhibits noteworthy disparities, and there is a scarcity of longitudinal studies. Furthermore, ASD manifests considerable heterogeneity, and the existing sample sizes may not suffice for a more nuanced patient stratification, potentially resulting in disparate outcomes despite similar sample sizes. Additionally, the utilization of diverse imaging equipment may introduce notable biases. Considering these factors, we contend that the current body of research on disparities in retinal sublayers between individuals with ASD and their typically developing counterparts lacks substantial comparative relevance, even when their findings diverge.

Understanding retinal abnormalities in ASD: potential mechanisms

Retinal nuclear layers, such as GCL and INL, are recognized as a paradigm of GM. Extensive ASD research reveals structural changes in GM (41) as well as atypical visual processing (42). Here, we explore the mechanisms behind thickened retinal layers, focusing on well-established functional alterations in ASD. Notably, OCT research primarily shows structural changes. Thus, the discussion on potential mechanisms related to retinal alterations remains speculative, aiming at providing additional perspectives within the emerging field.

The excitatory/inhibitory (E/I) imbalance theory in autism highlights γ-aminobutyric acid (GABA) and glutamate roles (43,44). Immunohistochemistry studies show GABA and glutamate in GCL and INL, impacting retinal responsiveness (45). An ASD rat model study reported the GABA reduction and mGluR5 increase affect visual information processing (46). And the GABAergic system has been reported to modulate retinal function differently in autistic and typically developed individuals (20). Based on our findings, we hypothesize that GABA/glutamate imbalance may influence synaptic function, potentially leading to the thickening of specific intraretinal layers, such as INL and GCL.

Mitochondrial dysfunction is postulated to play a pivotal role in the pathophysiology of ASD (47-49), with ASD even being considered as part of a broader spectrum of

mitochondrial diseases (50,51). Mitochondrial dysfunction affects adenosine triphosphate production and causing oxidative stress. Neuroimaging studies confirm altered glucose metabolism and increased oxidative stress in ASD brains (52-55). The retina's complex electrophysiological processes require precise energy supply, and mitochondrial dysfunction may disrupt retinal homeostasis, potentially altering retinal structure.

Immune damage and neuroinflammation play key roles in ASD pathogenesis. Abnormal activation of microglia and astrocytes is linked to enhanced immune responses and synaptic regulation in ASD brains (56-62). Microglia and astrocytes distribute across multiple retinal sublayers (63), potentially contributing to the thickening of GCL and INL.

Intraretinal layer thickness as a potential biomarker for ASD

This study did not find a significant correlation or predictive relationship between retinal sublayer thickness in the ASD group and the severity of core ASD symptoms measured by the total SRS score. However, the limited association between retinal thickness and social functioning in ASD, alongside the variability in social impairments and potential biases from partial clinical data exclusions, suggests caution in interpreting these results. Despite this, the study hints at potential for using retinal layer thickness as an ASD biomarker, encouraging future research with larger, stratified samples to explore simpler diagnostic methods.

Interestingly, we observed a positive correlation between the infero-nasal INL thickness and the cognitive level measured by the total IQ score. Moreover, the overall INL thickness demonstrated potential for predicting cognitive functioning. This suggests a potential coupling between global or localized INL thickness and cognitive function. Previous research also highlights a higher prevalence of intellectual disabilities in ASD populations, underscoring the relevance of investigating INL thickness as a predictor of cognitive abilities in autism (64-68). These findings imply that INL thickness may hold research potential within the hierarchical context of cognitive impairments in autism, providing inspiration for future investigations.

Limitations & future directions

The retina of individuals with ASD remains an area with limited comprehensive research. To address the heterogeneity of ASD, it is imperative to conduct stratified research and longitudinal analysis based on an expanded sample size. In light of the potential for multiple comparison corrections to introduce false-negative results beyond the anticipated level (69), this study cautiously emphasizes exploration of unadjusted results while also presenting statistically corrected significant findings to uphold diverse interpretations of the results. Notably, the statistical significance in this paper was explored under the resolution of the OCT device, meaning differences below 5 μm were not taken into consideration.

Given the strong gender bias towards males in ASD, the number of female samples is relatively small in all known related studies. In our study, we equalized the gender ratio between the ASD and NT groups to potentially account for any gender-related differences. However, future research considering gender as a subgroup is worth exploration. Additionally, the integration of multimodal data is essential for a comprehensive exploration of the retina from various perspectives. For example, optical coherence tomography angiography (OCTA) technology is able to provide information on blood flow, which naturally register and complement with OCT. Furthermore, abnormalities in brain lateralization provide valuable insights into the neural basis and developmental mechanisms of autism, which is possibly projected to the differences in interocular asymmetry between autism and control groups, making it a pertinent area of interest for our future work.

Conclusions

In this study, we enlarged the range of intraretinal layers from only the RNFL to almost all the retinal sublayer of peripapillary region, compared to previous studies. The expanded sample size might mitigate the data randomness, enhancing the reliability of the experimental results to some extent. This study was conducted in 47 children aged 7 to 13 with ASD and a well-matched control group in terms of number, age, and gender. We found statistically significant thickening in global GCL and INL in ASD subjects, suggesting a structural retinal change in children with ASD. Furthermore, we performed quadrant-wise analysis and observed increased thickness in the GCL in the nasal, inferior-temporal, and temporal quadrants, while the INL showed thickening in the nasal, inferior-nasal, inferior-temporal, and temporal quadrants in ASD group. Meanwhile, the inferior-nasal thickness of INL demonstrated a correlation with the total IQ scores.

The stepwise regression model revealed that the global thickness of INL exhibited effective fitting for the IQ scores in individuals with ASD. No significant correlation or predictive power was observed between the thickness of intraretinal layers and the total SRS scores. This study provides additional evidence for exploring the retina as a potential biomarker for ASD and may provide new directions for further investigation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-753/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-753/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Nanjing Medical University (Approval ID: 2020-SR-363). Informed consent was obtained from the participants' parents or guardians.

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