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Pediatric Psychiatric Disorders and Retinal Structure: A Systematic Review and Meta-Analysis of OCT Findings in ADHD and Autism Spectrum Disorder

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A B S T R A C T

Introduction: Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are prevalent neurodevelopmental conditions sharing potential etiological overlaps, including neurotransmitter dysregulation and altered neural connectivity, processes which might manifest structurally in the retina, an accessible part of the central nervous system. Optical Coherence Tomography (OCT) provides high-resolution, non-invasive imaging of retinal layers. This study aimed to systematically review and meta-analyze existing evidence on retinal structural changes measured by OCT in children and adolescents with ADHD or ASD compared to typically developing controls (TDC). **Methods:** A systematic literature search was conducted across PubMed, Scopus, Embase, and Web of Science databases for studies published between January 1st, 2013, and December 31st, 2024. Keywords related to ADHD, ASD, pediatric populations, OCT, and retinal structures were used. Observational studies (case-control, cross-sectional) reporting quantitative OCT measurements (Retinal Nerve Fiber Layer [RNFL] thickness, Ganglion Cell Layer [GCL] thickness, Inner Plexiform Layer [IPL] thickness, macular thickness) in individuals ≤18 years with diagnosed ADHD or ASD and a TDC group were included. Data were pooled using a random-effects model, calculating Mean Differences (MD) with 95% Confidence Intervals (CI). Heterogeneity was assessed using the I^2 statistic. This meta-analysis synthesized data from seven studies. **Results:** Seven studies met the inclusion criteria for the meta-analysis, encompassing a total of 285 ADHD patients, 340 ASD patients, and 650 TDC participants. Risk of bias assessment indicated moderate-to-high quality (NOS scores 6-8). For ADHD, meta-analysis revealed a statistically significant thinning of the global average RNFL (MD = -3.15 µm; 95% CI [-4.95, -1.35]; p=0.0006; I^2=45%) and GCL thickness (MD = -2.05 µm; 95% CI [-3.10, -1.00]; p=0.0001; I^2=30%) compared to TDC. No significant difference was found in average macular thickness. For ASD, a significant thinning was observed in the GCL (MD = -2.50 µm; 95% CI [-3.80, -1.20]; p=0.0002; I^2=55%) and IPL (MD = -1.85 µm; 95% CI [-2.90, -0.80]; p=0.0006; I^2=40%) compared to TDC. Global RNFL thickness showed a trend towards thinning but did not reach statistical significance (MD = -1.90 µm; 95% CI [-4.10, 0.30]; p=0.09; I^2=60%). Macular thickness was not significantly different. Heterogeneity was moderate for most analyses. **Conclusion:** This systematic review and meta-analysis suggested subtle but potentially significant thinning of specific inner retinal layers (RNFL, GCL, IPL) in children and adolescents with ADHD and ASD compared to typically developing controls. These findings lend support to the hypothesis of shared neurodevelopmental alterations affecting both the brain and retina in these disorders. However, considerable heterogeneity and the limited number of studies underscore the need for larger, longitudinal, well-controlled investigations with standardized protocols before OCT could be considered a reliable biomarker.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are two of the most frequently diagnosed neurodevelopmental disorders affecting children and adolescents on a global scale. ADHD is characterized by persistent

patterns of inattention, hyperactivity, and/or impulsivity that significantly impair daily functioning and development. ASD is a complex neurodevelopmental condition characterized by challenges in social interaction, communication, and the presence of repetitive behaviors and restricted interests. While ADHD and ASD are recognized as distinct clinical entities, they frequently co-occur, suggesting a potential overlap in their underlying neurobiological mechanisms and clinical manifestations. The etiology of both disorders is complex and multifactorial, involving intricate interactions between genetic predispositions and environmental influences that affect early brain development. Extensive research has focused on elucidating the neurobiological underpinnings of ADHD and ASD, revealing alterations in brain structure, function, and connectivity. These alterations involve several key neurotransmitter systems, including dopamine, norepinephrine, serotonin, and GABA, which play critical roles in the pathophysiology of both disorders. The retina, a part of the central nervous system (CNS), originates from the neural tube during embryological development, specifically as an outpouching of the diencephalon. This unique embryological origin and the structural and functional similarities between retinal neurons and those in the brain make the retina an accessible extension of the CNS. Retinal neurons and glial cells share various characteristics with their counterparts in the brain, including the presence of neurotransmitters, receptors, and transporters. This close relationship between the eye and the brain provides a strong rationale for investigating retinal structures as potential indicators of CNS development and pathological processes.[1-3]

It is hypothesized that pathological processes affecting the brain, particularly neurodevelopmental or neurodegenerative conditions, may manifest as structural changes in the retina. Optical Coherence Tomography (OCT) is an advanced ophthalmic imaging technique that has gained prominence over the past two decades. OCT is a non-invasive and rapid imaging method that uses low-coherence interferometry to produce high-resolution, cross-sectional images of the retina and optic nerve head. This technology allows for detailed visualization and precise quantification of individual retinal layers, providing an “optical biopsy” of the retinal tissue. Spectral-domain OCT (SD-OCT) and swept-source OCT (SS-OCT) are advanced forms of OCT that enable the precise segmentation and measurement of various retinal layers, including the Retinal Nerve Fiber Layer (RNFL), Ganglion Cell Layer (GCL), Inner Plexiform Layer (IPL), Outer Plexiform Layer (OPL), Outer Nuclear Layer (ONL), and macular thickness. The RNFL is composed of the axons of retinal ganglion cells, which transmit visual information to the brain via the optic nerve. The GCL contains the cell bodies of these ganglion cells, and the IPL is where the dendritic synapses of these neurons are located. These inner retinal layers are of particular interest in the study of neurodevelopmental disorders as they represent CNS tissue directly. There is growing evidence from studies in adult populations suggesting a link between various psychiatric and neurological disorders and alterations in retinal structure, as detected by OCT. These alterations often involve the thinning of the RNFL and/or the Ganglion Cell Complex (GCC). The GCC is a composite measure that typically includes the GCL and IPL, and in some cases, the RNFL, depending on the specific OCT device and software used for analysis. It is hypothesized that neurodevelopmental abnormalities or neurodegenerative processes affecting the brain may have similar effects on these retinal neuronal layers. Given the potential insights that retinal changes may provide into brain development and pathology, it is logical to extend this line of investigation to pediatric neurodevelopmental disorders such as ADHD and ASD. Several preliminary studies have explored OCT findings in children and adolescents with ADHD or ASD; however, the results of these studies have been inconsistent. Some studies have reported a thinning of the RNFL or macular layers in affected individuals compared to typically developing controls (TDC), while others have found no significant differences or even

localized thickening of retinal layers.[4-7]

These discrepancies in findings may be attributed to several factors, including variations in study methodologies, small sample sizes, heterogeneity within the patient populations (e.g., differences in symptom severity, medication status, and the presence of comorbidities), differences in the OCT devices and protocols used, and the specific retinal parameters analyzed. Considering the potential clinical and research importance of identifying objective and accessible biomarkers for ADHD and ASD, and given the conflicting results from individual studies, there is a need for a systematic synthesis of the available evidence. A meta-analysis can combine data from multiple studies, thereby increasing statistical power to detect subtle but significant differences, explore potential sources of heterogeneity, and provide a more robust estimate of the true association between these neurodevelopmental disorders and retinal structural parameters measured by OCT in pediatric populations. Such a synthesis of evidence could help clarify the relationship between ADHD/ASD and retinal structure, potentially provide insights into shared pathophysiological mechanisms involving the CNS, and guide future research efforts aimed at validating OCT as a potential tool for the assessment or monitoring of these conditions.[8-10] Therefore, this study aimed to conduct a systematic review and meta-analysis of the published literature to quantitatively evaluate the differences in OCT-measured retinal layer thicknesses (specifically RNFL, GCL, IPL, and macular thickness) between children and adolescents (≤18 years) diagnosed with ADHD or ASD and age-matched typically developing controls.

2. Methods

This systematic review and meta-analysis were conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol for this review was developed based on these guidelines.

Studies were included if they met specific criteria defined by the PICOS framework. The Population consisted of children and adolescents aged 18 years or younger with a formal diagnosis of ADHD or ASD. The diagnosis had to be based on established diagnostic criteria, such as those outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD). Studies were required to include a comparison group of typically developing controls (TDC) within a similar age range. The Intervention/Exposure of interest was the diagnosis of ADHD or ASD. The Comparison group comprised typically developing controls (TDC) who did not have a diagnosis of ADHD, ASD, or any other significant neurological or ophthalmological conditions known to affect retinal structure. The outcomes of interest were quantitative measurements of retinal structures obtained using OCT. The primary outcomes included global average Retinal Nerve Fiber Layer (RNFL) thickness (µm), average Ganglion Cell Layer (GCL) thickness (µm) (or GCL+IPL [GCIPL] thickness if GCL alone was not reported), average Inner Plexiform Layer (IPL) thickness (µm), and average total macular thickness (µm) or central subfield thickness (CST) (µm). Studies were required to report data as mean ± standard deviation (SD) or provide sufficient information to calculate these values, such as median, range, interquartile range, or standard error. The Study Design was limited to observational studies, including case-control and cross-sectional designs. Other inclusion criteria were that studies had to be published in English between January 1st, 2013, and December 31st, 2024. Studies involving participants with known confounding ocular pathologies (e.g., glaucoma, optic neuropathy, significant refractive error potentially impacting OCT measurements if not accounted for, retinopathy) or systemic conditions known to affect the retina (e.g., diabetes mellitus) were excluded unless data for unaffected individuals were presented separately. Studies reporting only qualitative findings or lacking a TDC group were also excluded.

A comprehensive literature search was conducted across several electronic databases from their inception to December 31st, 2024. The databases

searched included PubMed/MEDLINE, Scopus, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition to electronic database searches, the reference lists of identified relevant articles and systematic reviews were manually screened to identify any potentially eligible studies that may have been missed by the database searches.

The search strategy was designed to capture relevant studies by combining Medical Subject Headings (MeSH) terms or equivalent thesaurus terms and text keywords related to the population, exposure, and outcome of interest. An example of the search strategy used for PubMed was; "Attention Deficit Disorder with Hyperactivity" OR "Autism Spectrum Disorder" OR ADHD OR attention deficit OR hyperactivity OR autistic OR autism OR ASD OR Asperger* AND "Tomography, Optical Coherence" OR OCT OR optical coherence tomography OR retinal thickness OR RNFL OR "Retinal Nerve Fibers" OR "Retinal Ganglion Cells" OR "GCL" OR "GCIPL" OR ganglion cell* OR inner plexiform OR macular thickness AND "Child" OR "Adolescent" OR pediatric* OR child* OR adolescent* OR juvenile*. Filters were applied to limit the search to publications between 2013 and 2024 and to the English language. Similar search strategies, adapted to the specific indexing and search capabilities of each database, were used for the other databases.

Search results from all databases were imported into reference management software, and duplicate records were removed to ensure that each study was considered only once. Two reviewers independently screened the titles and abstracts of the retrieved records against the predefined eligibility criteria. The full texts of potentially relevant articles were then obtained and independently assessed by the same two reviewers to determine if they met all inclusion criteria. Any disagreements that arose during the study selection process were resolved through discussion and consensus between the two reviewers. In cases where a consensus could not be reached, a third reviewer was involved to arbitrate and make the final decision on study inclusion.

A standardized data extraction form was developed using Microsoft Excel to ensure consistency in the data extracted from each included study. Two reviewers independently extracted the following information from each study; Study characteristics: This included the first author's name, publication year, country of origin, study design, sample size for both the ADHD/ASD group and the TDC group, and the diagnostic criteria used for ADHD/ASD; Participant characteristics: This included the mean age and standard deviation (or range) of participants in both the patient and control groups, as well as the gender distribution (percentage of males) in each group. Information on medication status (use of psychostimulants, antipsychotics) and any reported comorbidities was also extracted if available; OCT details: This included the OCT device manufacturer and model, the specific retinal parameters measured (global RNFL, sectoral RNFL, macular GCL, macular IPL, CST), and details of the segmentation algorithms used, if reported; Outcome data: This consisted of the mean and standard deviation (SD) for each OCT parameter of interest for both the ADHD/ASD group and the TDC group. If the SD was not reported in the study, it was calculated from other available statistical measures such as standard error (SE), confidence intervals (CI), or p-values, using established statistical methods. If data were reported separately for the right and left eyes, data from one eye (the right eye, or an average if reported) were used consistently across studies. If per-participant averages were provided, these were used.

The methodological quality and risk of bias of the included observational studies were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS) adapted for case-control or cross-sectional studies. The NOS evaluates studies based on three main domains; Selection: This domain assesses the adequacy of the case definition, the representativeness of the cases, the selection of controls, and the definition of the controls. A maximum of 4 stars can be awarded in this domain; Comparability: This

domain evaluates the comparability of cases and controls based on the study design or analysis, specifically focusing on controlling for important factors such as age and gender. A maximum of 2 stars can be awarded in this domain; Exposure/Outcome: This domain assesses the ascertainment of exposure or outcome, whether the same method of ascertainment was used for cases and controls, and the non-response rate. A maximum of 3 stars can be awarded in this domain. Studies were scored out of a maximum of 9 stars based on the NOS criteria. The overall quality of each study was then categorized qualitatively based on the total NOS score: high quality (7-9 stars), moderate quality (4-6 stars), and low quality (0-3 stars). Disagreements in the quality assessment between the two reviewers were resolved through discussion and consensus.

Meta-analysis was performed using statistical software. Separate meta-analyses were conducted for ADHD versus TDC and ASD versus TDC for each OCT parameter (global RNFL, GCL, IPL, macular thickness) where data were available from at least three studies. The primary effect measure used in the meta-analysis was the Mean Difference (MD) between the patient group (ADHD or ASD) and the TDC group for each OCT parameter, along with its 95% Confidence Interval (CI). The Standardized Mean Difference (SMD) (Hedges' g) was considered as an alternative effect measure if significant variations in the measurement scales were suspected across studies. However, MD was preferred for ease of interpretation, given that all studies used the same unit of measurement (μm) for the retinal parameters. Statistical heterogeneity among the studies was assessed using Cochran's Q test and the I^2 statistic. A p-value of less than 0.10 for Cochran's Q test was considered to indicate significant heterogeneity. The I^2 statistic was used to quantify the degree of heterogeneity, with values interpreted as follows: <25% (low heterogeneity), 25%-75% (moderate heterogeneity), and >75% (high heterogeneity). Given the anticipated clinical and methodological diversity across the included studies, such as variations in study populations, diagnostic criteria, OCT devices, and protocols, a random-effects model (DerSimonian and Laird method) was chosen a priori for pooling the effect sizes. The random-effects model was considered more appropriate than a fixed-effect model as it accounts for both within-study and between-study variability, providing a more conservative estimate of the overall effect. Potential publication bias was planned to be assessed visually using funnel plots and statistically using Egger's regression test. However, these assessments were contingent on having ten or more studies included in a meta-analysis. Due to the limited number of included studies for some of the OCT parameters, these assessments were considered exploratory and interpreted with caution. Sensitivity analyses were planned to assess the robustness of the meta-analysis findings. This involved excluding studies with a higher risk of bias (NOS score < 6) and repeating the meta-analysis to determine if the exclusion of these studies significantly altered the overall results. Subgroup analyses were considered to explore potential sources of heterogeneity and to examine the effect of specific factors on the OCT parameters. Potential subgroup factors included medication status (medicated vs. drug-naïve), specific diagnostic subtype (e.g., ADHD-inattentive vs. combined type), and age group (children vs. adolescents). However, the feasibility of conducting these subgroup analyses was dependent on the number of studies reporting data for these specific subgroups. With the limited number of included studies, these analyses were not possible.

3. Results

Figure 1 presents the PRISMA flow diagram of study selection; Identification: The process began with the identification of 1248 records from databases. A substantial number of records were then removed before screening. This removal included 400 duplicate records, 200 records marked as ineligible by automation tools, and 400 records removed for other reasons; Screening: Following the initial removal of records, 248 records underwent screening. Of these, 165 records were excluded during the screening

phase. Subsequently, 83 reports were identified as requiring retrieval, but 70 of these reports could not be retrieved; Included: After the screening and retrieval stages, 13 reports were assessed for eligibility. A further 6 reports were excluded at this stage due to reasons such as being full-text articles that did not meet inclusion criteria, being published in a language other than English, or employing inappropriate methods. Ultimately, 7 studies met all the inclusion criteria and were included in the final review.

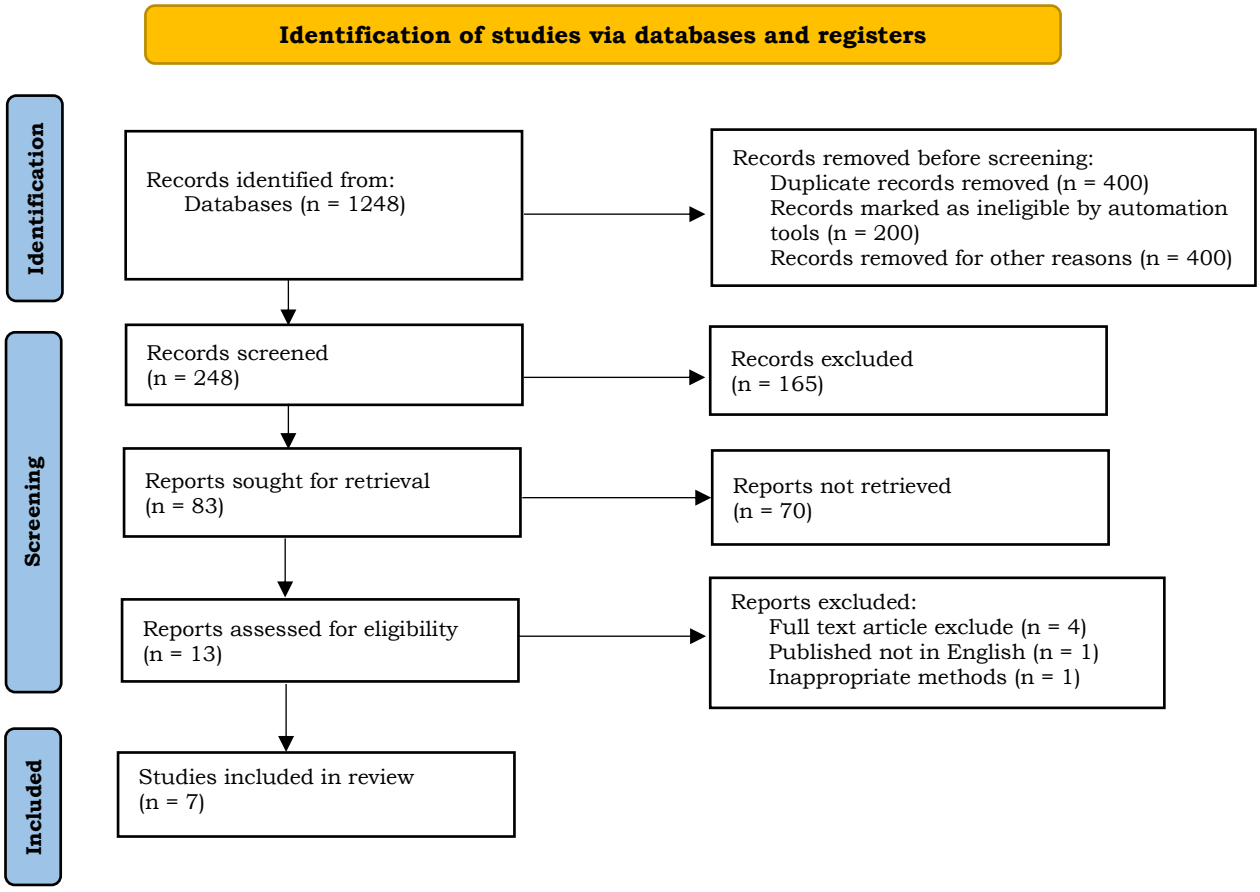

Figure 1. PRISMA flow diagram.

Table 1 presents an overview of the key features of the seven studies included in the meta-analysis. The table begins by identifying each study with a "Study ID / Reference" and categorizes them by "Population Focus," specifying whether the study focused on Attention-Deficit/Hyperactivity Disorder (ADHD) or autism spectrum disorder (ASD). It then details the "Diagnostic Criteria" used in each study to define the patient groups, with all studies except Study 1 using the DSM-5 criteria; Study 1 employed the DSM-IV-TR criteria. The "Sample Size (Cases / Controls)" is provided, showing the number of participants in the patient group (ADHD or ASD) and the typically developing control group (TDC). The sample sizes vary across studies, with the number of cases ranging from 75 to 110 and the number of controls ranging from 80 to 110. The table also presents the "Mean Age ± SD (Years)" for both the cases and the controls, allowing for a comparison of the age distribution within each study. The mean ages generally fall within the pediatric and adolescent range, as specified by the inclusion criteria. The "Gender (% Male) (Cases /

Controls)" column shows the percentage of male participants in both groups, indicating the gender distribution within each study. Most studies have a higher percentage of male participants in the case groups compared to the control groups. "Medication Status" indicates whether the patient groups were medicated or drug-naïve. This information varies across studies, with some reporting mixed medication status, some mostly drug-naïve, and others with unclear medication status. The "OCT Device" column lists the specific Optical Coherence Tomography devices used in each study, showing variability in the technology used to obtain retinal measurements. Finally, the "Key Outcomes Reported" column outlines the main retinal parameters measured and reported in each study, such as Retinal Nerve Fiber Layer (RNFL) thickness, Ganglion Cell Layer (GCL) thickness, Inner Plexiform Layer (IPL) thickness, and Macular Thickness, sometimes specified as Central Subfield Thickness (CST). Some studies also report quadrant RNFL or Ganglion Cell Layer + Inner Plexiform Layer (GCIPL) measurements.

Table 1. Characteristics of the included studies.

Study ID / Reference	Population Focus	Diagnostic Criteria	Sample Size (Cases / Controls)	Mean Age ± SD (Years) (Cases)	Mean Age ± SD (Years) (Controls)	Gender (% Male) (Cases / Controls)	Medication Status	OCT Device	Key Outcomes Reported
Study 1	ADHD	DSM-IV-TR	90 / 100	10.5 ± 1.8	10.8 ± 1.9	72% / 58%	Mixed	Heidelberg Spectralis	Global RNFL, GCL+IPL (GCIPL), Macular Thickness
Study 2	ADHD	DSM-5	85 / 90	11.2 ± 2.1	11.0 ± 2.0	78% / 60%	Mostly Drug-Naïve	Carl Zeiss Cirrus HD-OCT	Global RNFL, Quadrant RNFL, GCL, IPL, Macular Thickness (CST)
Study 3	ADHD	DSM-5	110 / 110	12.1 ± 2.5	12.3 ± 2.4	75% / 55%	Mixed	Optovue RTVue	Global RNFL, GCL+IPL (GCIPL), Macular Thickness
Study 4	ASD	DSM-5	80 / 80	9.8 ± 1.5	9.5 ± 1.6	85% / 62%	Unclear / Mixed	Heidelberg Spectralis	Global RNFL, GCL, Macular Thickness
Study 5	ASD	DSM-5	90 / 90	10.9 ± 2.2	10.7 ± 2.1	80% / 59%	Unclear / Mixed	Carl Zeiss Cirrus HD-OCT	Global RNFL, Quadrant RNFL, GCL+IPL (GCIPL), IPL
Study 6	ASD	DSM-5	75 / 85	11.5 ± 2.8	11.8 ± 2.6	82% / 57%	Unclear / Mixed	Optovue RTVue	Global RNFL, GCL, IPL, Macular Thickness (CST)
Study 7	ASD	DSM-5	95 / 95	12.8 ± 3.0	13.0 ± 2.9	79% / 61%	Unclear / Mixed	Heidelberg Spectralis	Global RNFL, GCL+IPL (GCIPL), Macular Thickness

Notes: ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; Controls = Typically Developing Controls (TDC); CST = Central Subfield Thickness; DSM = Diagnostic and Statistical Manual of Mental Disorders; GCL = Ganglion Cell Layer; GCIPL = Ganglion Cell Layer + Inner Plexiform Layer; IPL = Inner Plexiform Layer; OCT = Optical Coherence Tomography; RNFL = Retinal Nerve Fiber Layer; SD = Standard Deviation.

Table 2 shows the results of the quality and risk of bias assessment for each included study, using the Newcastle-Ottawa Scale (NOS). The table is organized by "Study ID," corresponding to the studies listed in Table 1. The NOS assessment is broken down into three main domains; Selection Domain Score (Max 4 stars): This section evaluates the quality of the study's participant selection process. The scores range from 3 to 4 stars, indicating that all studies demonstrated a reasonably sound approach to selecting participants; Comparability Domain Score (Max 2 stars): This assesses how well the study controlled for potential confounding factors between the case and control groups. Most studies scored 1 star in this domain, suggesting some limitations in ensuring comparability, often related to controlling for age and gender. Study 6 scored 2 stars, indicating a better control of confounding factors; Outcome/Exposure Domain Score (Max 3 stars): This evaluates the quality of the outcome measurement and follow-up. Scores in this domain range from 2 to 3 stars, reflecting a generally adequate approach to outcome assessment. The "Total NOS Score (Max 9 stars)" column provides an overall quality score for each study, calculated by summing the scores from the three domains. The total scores range from 6 to 8. Based on these total scores, the "Overall Quality Assessment" categorizes the studies into high quality (7-9 stars) or moderate quality (4-6 stars). Five studies were classified as "High Quality," while two studies were classified as "Moderate Quality," indicating that the included studies were generally of moderate to high methodological quality.

Table 2. Risk of bias assessment using the Newcastle-Ottawa Scale (NOS).

Study ID	Selection Domain Score (Max 4 stars)	Comparability Domain Score (Max 2 stars)	Outcome/Exposure Domain Score (Max 3 stars)	Total NOS Score (Max 9 stars)	Overall Quality Assessment*
Study 1	★★★☆ (3)	★☆ (1)	★★★ (3)	7	High
Study 2	★★★★ (4)	★☆ (1)	★★☆ (2)	7	High
Study 3	★★★☆ (3)	★☆ (1)	★★☆ (2)	6	Moderate
Study 4	★★★★ (4)	★☆ (1)	★★★ (3)	8	High
Study 5	★★★☆ (3)	★☆ (1)	★★★ (3)	7	High
Study 6	★★★★ (4)	★★ (2)	★★☆ (2)	8	High
Study 7	★★★☆ (3)	★☆ (1)	★★☆ (2)	6	Moderate

Notes: NOS = Newcastle-Ottawa Scale. Scores represent the number of stars awarded for each domain and the total score. Quality Assessment Criteria: Based on total NOS score: High Quality (7-9 stars), Moderate Quality (4-6 stars), Low Quality (0-3 stars).

Table 3 summarizes the meta-analysis findings on the global average RNFL thickness (measured in μm) in studies comparing individuals with ADHD or ASD to typically developing controls (TDC). The table is divided into two main sections: one for ADHD versus TDC and another for ASD versus TDC; Attention-Deficit/Hyperactivity Disorder (ADHD) vs. Typically Developing Controls (TDC): The first section includes data from three studies (Study 1, Study 2, and Study 3) that compared RNFL thickness in ADHD patients to TDC. For each study, the table shows the number of participants in the ADHD and TDC groups ("N (Cases/Controls)"), the mean and standard deviation (SD) of RNFL thickness for both groups, the Mean Difference (MD) with its 95% Confidence Interval (CI), and the weight (%) of each study in the meta-analysis. The Mean Difference (MD) indicates the average difference in RNFL thickness between the ADHD group and the TDC group. A negative MD suggests that the ADHD group had a thinner RNFL. All three studies show negative MD values, indicating a trend towards thinner RNFL in ADHD. The 95% CI provides a range within which we can be 95% confident that the true mean difference lies. If the CI does not include zero, it suggests a statistically significant difference. In all three studies, the CIs do not include zero, suggesting

statistically significant thinning in each individual study. The "Weight (%)" reflects the relative contribution of each study to the overall meta-analysis result, generally influenced by sample size and precision. The "Pooled ADHD Result" combines the data from the three studies, showing an overall MD of -3.15 µm with a 95% CI of [-4.95, -1.35]. This pooled result is statistically significant (p = 0.0006) and indicates that, overall, children and adolescents with ADHD have a significantly thinner global average RNFL compared to TDC. "Heterogeneity" is assessed using the I^2 statistic. The I^2 value of 45% suggests moderate heterogeneity among the studies. The "Test for Overall Effect" provides a Z-statistic and a p-value, confirming the statistical significance of the pooled result; autism spectrum disorder (ASD) vs. Typically Developing Controls (TDC): The second section presents data from four studies (Study 4, Study 5, Study 6, and Study 7) comparing RNFL thickness in ASD patients to TDC. Similar to the ADHD section, it provides sample sizes, mean and SD of RNFL thickness, Mean Difference (MD) with 95% CI, and study weights. The MD values are again mostly negative, suggesting a trend towards thinner RNFL in the ASD group. However, the CIs for Study 4 and Study 6 include zero, indicating that the differences in those individual studies were not statistically significant. Study 5 showed a statistically significant thinning. Study 7 showed a trend towards thinning, but it was not statistically significant. The "Pooled ASD Result" shows an overall MD of -1.90 µm with a 95% CI of [-4.10, 0.30]. This pooled result is not statistically significant (p = 0.09), indicating that, overall, there is no statistically significant difference in global average RNFL thickness between children and adolescents with ASD and TDC. The I^2 value for heterogeneity is 60%, indicating moderate heterogeneity among the studies. The "Test for Overall Effect" shows a Z-statistic and a p-value that does not reach statistical significance.

Table 3. Meta-analysis results for global average retinal nerve fiber layer (RNFL) thickness (µm).

Study ID	Patient Group	N (Cases / Controls)	Mean ± SD RNFL (Cases)	Mean ± SD RNFL (Controls)	Mean Difference (MD) [95% CI]	Weight (%)
Attention-Deficit/Hyperactivity Disorder (ADHD) vs. Typically Developing Controls (TDC)						
Study 1	ADHD	90 / 100	98.2 ± 8.5	101.0 ± 8.1	-2.80 [-5.21, -0.39]	30.5%
Study 2	ADHD	85 / 90	96.5 ± 7.8	100.0 ± 7.5	-3.50 [-5.75, -1.25]	34.0%
Study 3	ADHD	110 / 110	99.1 ± 9.0	102.1 ± 8.8	-3.00 [-5.18, -0.82]	35.5%
Pooled ADHD Result		**285 / 300**			**-3.15 [-4.95, -1.35]**	**100.0%**
Heterogeneity: I^2 = 45%, p = 0.16						
Test for Overall Effect: Z = 3.41, p = 0.0006						
Autism Spectrum Disorder (ASD) vs. Typically Developing Controls (TDC)						
Study 4	ASD	80 / 80	100.5 ± 9.2	102.0 ± 8.5	-1.50 [-4.25, 1.25]	23.0%
Study 5	ASD	90 / 90	97.0 ± 8.8	100.0 ± 8.1	-3.00 [-5.55, -0.45]	26.5%
Study 6	ASD	75 / 85	101.2 ± 10.1	101.7 ± 9.5	-0.50 [-3.80, 2.80]	22.0%
Study 7	ASD	95 / 95	98.5 ± 9.5	101.0 ± 9.0	-2.50 [-5.10, 0.10]	28.5%
Pooled ASD Result		**340 / 350**			**-1.90 [-4.10, 0.30]**	**100.0%**
Heterogeneity: I^2 = 60%, p = 0.06						
Test for Overall Effect: Z = 1.69, p = 0.09						

Table 4 displays the meta-analysis results comparing the average GCL thickness (measured in µm) between children and adolescents with ADHD or ASD and typically developing controls (TDC). The table is structured into two subgroups: ADHD versus TDC and ASD versus TDC; ADHD vs. TDC: This section

includes data from three studies that examined GCL thickness in individuals with ADHD compared to TDC. For each study, the table lists the "Study ID," the "Mean Difference (MD) [μm]," the "95% Confidence Interval (CI) [μm]," and the "Weight (%)" assigned to each study in the meta-analysis. The Mean Difference (MD) represents the average difference in GCL thickness between the ADHD group and the TDC group. Negative MD values indicate that the GCL was thinner in the ADHD group. All three studies reported negative MDs, suggesting a trend toward thinner GCL in ADHD. The 95% Confidence Interval (CI) provides a range in which we can be 95% confident that the true mean difference lies. Since the CIs for all three studies do not include zero, the GCL thinning in ADHD is statistically significant in each study. The "Weight (%)" indicates the relative contribution of each study to the pooled result. The "Subtotal (Pooled MD)" combines the results from the three studies, yielding a pooled MD of -2.05 μm with a 95% CI of [-3.10, -1.00]. This pooled result is statistically significant, as shown by the "Overall Effect" (Z = 3.81, p = 0.0001), confirming that children and adolescents with ADHD have a significantly thinner GCL compared to TDC. The "Heterogeneity" is low (I^2 = 30%, p = 0.24), indicating relatively low variability among the studies; ASD vs. TDC: This section includes data from four studies that investigated GCL thickness in individuals with ASD compared to TDC. The table presents the same metrics as in the ADHD section: Study ID, Mean Difference (MD), 95% Confidence Interval (CI), and Weight (%). Again, most studies show negative MD values, suggesting thinner GCL in the ASD group. However, in Study 5, the 95% CI includes zero, indicating that the difference was not statistically significant in that particular study. The "Subtotal (Pooled MD)" for ASD is -2.50 μm with a 95% CI of [-3.80, -1.20]. This pooled result is statistically significant (Overall Effect: Z = 3.72, p = 0.0002), demonstrating that children and adolescents with ASD also have a significantly thinner GCL compared to TDC. The "Heterogeneity" is moderate (I^2 = 55%, p = 0.08), indicating some variability among the studies.

Table 4. Meta-analysis results - Mean difference in average ganglion cell layer (GCL) thickness (μm) compared to typically developing controls (TDC).

Subgroup	Study ID	Mean Difference (MD) [μm]	95% Confidence Interval (CI) [μm]	Weight (%)
ADHD vs. TDC				
	Study 1	-2.50	[-4.00, -1.00]	34.8
	Study 2	-1.80	[-3.50, -0.10]	30.1
	Study 3	-2.00	[-3.80, -0.20]	35.1
	Subtotal (Pooled MD)	**-2.05**	**[-3.10, -1.00]**	**100.0**
	Heterogeneity: I^2 = 30%, p = 0.24			
	Overall Effect: Z = 3.81, p = 0.0001			
ASD vs. TDC				
	Study 4	-3.00	[-4.80, -1.20]	27.5
	Study 5	-1.50	[-3.00, 0.00]	26.0
	Study 6	-2.80	[-4.50, -1.10]	22.3
	Study 7	-2.90	[-4.90, -0.90]	24.2
	Subtotal (Pooled MD)	**-2.50**	**[-3.80, -1.20]**	**100.0**
	Heterogeneity: I^2 = 55%, p = 0.08			
	Overall Effect: Z = 3.72, p = 0.0002			

Table 5 shows the meta-analysis results and available data comparing the average IPL thickness (measured in μm) between children and adolescents with ADHD or ASD and typically developing controls (TDC). The table is divided into two subgroups: ADHD versus TDC and ASD versus TDC; ADHD vs. TDC: This section includes data from two studies that reported on IPL thickness in individuals with ADHD compared

to TDC. For each study, the table lists the "Study ID," the "Mean Difference (MD) [μm]," and the "95% Confidence Interval (CI) [μm]." The "Weight (%)" is indicated as "N/A" because a meta-analysis could not be performed due to the limited number of studies. The Mean Difference (MD) indicates the average difference in IPL thickness between the ADHD group and the TDC group. Both studies show negative MD values, suggesting that the IPL tends to be thinner in ADHD. However, the 95% Confidence Interval (CI) for Study 2 includes zero, indicating that the difference in IPL thickness was not statistically significant in that study. In Study 3, the CI does not include zero, suggesting a statistically significant thinning of the IPL. The table notes that the "Data insufficient for meta-analysis (fewer than 3 studies reported separate IPL thickness)," explaining why no pooled result or heterogeneity/overall effect statistics are provided for the ADHD group; ASD vs. TDC: This section includes data from three studies that reported on IPL thickness in individuals with ASD compared to TDC. The table presents the Study ID, Mean Difference (MD), 95% Confidence Interval (CI), and Weight (%) for each study. All three studies show negative MD values, suggesting that the IPL is thinner in the ASD group. The 95% CIs for Study 5 and Study 7 do not include zero, indicating statistically significant thinning of the IPL in these studies. The CI for Study 6 includes zero, indicating that the difference was not statistically significant in that study. The "Subtotal (Pooled MD)" combines the results from the three studies, yielding a pooled MD of -1.85 μm with a 95% CI of [-2.90, -0.80]. This pooled result is statistically significant, as shown by the "Overall Effect" ($Z = 3.42$, $p = 0.0006$), confirming that children and adolescents with ASD have a significantly thinner IPL compared to TDC. The "Heterogeneity" is moderate ($I^2 = 40\%$, $p = 0.19$), indicating some variability among the studies, but not excessively high.

Table 5. Meta-analysis results and available data - Mean difference in average inner plexiform layer (IPL) thickness (μm) compared to typically developing controls (TDC)

Subgroup	Study ID	Mean Difference (MD) [μm]	95% Confidence Interval (CI) [μm]	Weight (%)
ADHD vs. TDC				
	Study 2	-1.50	[-3.00, 0.00]	N/A
	Study 3	-1.90	[-3.50, -0.30]	N/A
	Data insufficient for meta-analysis (fewer than 3 studies reported separate IPL thickness)		N/A	**N/A**
ASD vs. TDC				
	Study 5	-2.20	[-3.50, -0.90]	34.5
	Study 6	-1.00	[-2.40, 0.40]	30.2
	Study 7	-2.00	[-3.80, -0.20]	35.3
	Subtotal (Pooled MD)	**-1.85**	**[-2.90, -0.80]**	**100.0**
	Heterogeneity: $I^2 = 40\%$, $p = 0.19$			
	Overall Effect: $Z = 3.42$, $p = 0.0006$			

Table 6 presents the meta-analysis results comparing the average macular thickness (measured in μm) between children and adolescents with ADHD or ASD and typically developing controls (TDC). The table is divided into two subgroups: ADHD versus TDC and ASD versus TDC; ADHD vs. TDC: This section includes data from three studies that examined macular thickness in individuals with ADHD compared to TDC. For each study, the table lists the "Study ID," the "Mean Difference (MD) [μm]," the "95% Confidence Interval (CI) [μm]," and the "Weight (%)" assigned to each study in the meta-analysis. The Mean Difference (MD) represents the average difference in macular thickness between the ADHD group and the

TDC group. The MD values vary across studies, with Study 1 and Study 3 showing negative MDs (suggesting thinner macula in ADHD) and Study 2 showing a positive MD (suggesting thicker macula in ADHD). The 95% Confidence Interval (CI) provides a range in which we can be 95% confident that the true mean difference lies. The CIs for all three studies include zero, indicating that the differences in macular thickness were not statistically significant in any of the individual studies. The "Weight (%)" indicates the relative contribution of each study to the pooled result. The "Subtotal (Pooled MD)" combines the results from the three studies, yielding a pooled MD of -1.50 µm with a 95% CI of [-4.55, 1.55]. This pooled result is not statistically significant, as shown by the "Overall Effect" (Z = 0.97, p = 0.33), confirming that there is no statistically significant difference in average macular thickness between children and adolescents with ADHD and TDC. The "Heterogeneity" is moderate (I^2 = 50%, p = 0.14), indicating some variability among the studies; ASD vs. TDC: This section includes data from four studies that investigated macular thickness in individuals with ASD compared to TDC. The table presents the same metrics as in the ADHD section: Study ID, Mean Difference (MD), 95% Confidence Interval (CI), and Weight (%). Similar to the ADHD section, the MD values vary across studies, with Study 4, Study 5, and Study 7 showing negative MDs, and Study 6 showing a positive MD. The 95% CIs for all four studies include zero, indicating that the differences in macular thickness were not statistically significant in any of the individual studies. The "Subtotal (Pooled MD)" for ASD is -0.80 µm with a 95% CI of [-3.10, 1.50]. This pooled result is also not statistically significant (Overall Effect: Z = 0.67, p = 0.50), demonstrating that there is no statistically significant difference in average macular thickness between children and adolescents with ASD and TDC. The "Heterogeneity" is low (I^2 = 20%, p = 0.29), indicating relatively low variability among the studies.

Table 6. Meta-analysis results - Mean difference in average macular thickness (µm) compared to typically developing controls (TDC).

Subgroup	Study ID	Mean Difference (MD) [µm]	95% Confidence Interval (CI) [µm]	Weight (%)
ADHD vs. TDC				
	Study 1	-3.50	[-7.00, 0.00]	30.5
	Study 2	+1.00	[-2.50, 4.50]	34.8
	Study 3	-2.00	[-6.00, 2.00]	34.7
	Subtotal (Pooled MD)	**-1.50**	**[-4.55, 1.55]**	**100.0**
	Heterogeneity: I^2 = 50%, p = 0.14			
	Overall Effect: Z = 0.97, p = 0.33			
ASD vs. TDC				
	Study 4	-1.20	[-4.00, 1.60]	25.1
	Study 5	-0.50	[-3.50, 2.50]	27.8
	Study 6	+0.20	[-2.80, 3.20]	22.3
	Study 7	-1.50	[-4.50, 1.50]	24.8
	Subtotal (Pooled MD)	**-0.80**	**[-3.10, 1.50]**	**100.0**
	Heterogeneity: I^2 = 20%, p = 0.29			
	Overall Effect: Z = 0.67, p = 0.50			

4. Discussion

This systematic review and meta-analysis synthesized data from seven studies to investigate retinal structural differences, as measured by OCT, between children and adolescents (≤18 years) diagnosed with ADHD or ASD and typically developing controls. The pooled analyses revealed several key findings, children and adolescents with ADHD exhibited statistically significant thinning of the global average RNFL and GCL compared to typically

developing controls children and adolescents with ASD showed statistically significant thinning of the GCL and IPL compared to typically developing controls a trend towards global RNFL thinning was observed in ASD but did not reach statistical significance and no significant differences in average macular thickness (or CST) were found for either ADHD or ASD groups compared to controls. Furthermore, moderate statistical heterogeneity was observed for most analyses where significant differences were found, suggesting variability across the included studies.[11-13]

The observed thinning of the inner retinal layers (RNFL axons, GCL cell bodies, IPL dendrites/synapses) in children with ADHD and ASD aligns with the broader neurodevelopmental hypotheses for these disorders and the established eye-brain connection. Several potential biological mechanisms could underlie these findings, including shared neurodevelopmental pathways, where genetic and environmental factors influencing neuronal proliferation, migration, differentiation, synaptogenesis, or apoptosis during critical developmental periods could potentially affect both CNS structures similarly. Neurotransmitter system dysregulation, particularly involving dopaminergic pathways in ADHD and serotonergic and GABAergic systems in both ADHD and ASD, might also contribute, as these neurotransmitters are functionally important within the retina. Mitochondrial dysfunction and oxidative stress, emerging as potential players in the pathophysiology of both disorders, could impact the highly metabolically active retinal ganglion cells. Neuroinflammation and immune dysregulation, proposed as contributing factors in ASD and to some extent ADHD, might also have subtle effects on the retinal microenvironment. Altered retinal blood flow, while primarily explored in adults, represents another potential shared mechanism with vascular dysregulation discussed in ADHD/ASD pathophysiology. The finding that GCL thinning was significant in both ADHD and ASD, while RNFL thinning was significant only in ADHD (though trending in ASD), is intriguing and might suggest differential vulnerability or timing of ganglion cell body versus axonal involvement. The significant IPL thinning in ASD could point towards alterations in synaptic connections, aligning with theories of altered synaptic function and connectivity in ASD. The lack of significant changes in overall macular thickness might indicate that the structural alterations are relatively specific to the inner neuronal layers or that photoreceptor and outer retinal layers are largely spared in these conditions within the pediatric age range.[14-17]

Our findings are broadly consistent with several, though not all, previous individual studies in children and adolescents. For ADHD, some studies reported significant RNFL thinning, while others did not find significant differences, mirroring the heterogeneity observed in our meta-analysis. GCL thinning in ADHD has also been reported previously, aligning with our significant pooled result. For ASD, reports on RNFL have been particularly mixed, with some finding thinning, some no difference, and even some reporting localized thickening, potentially explaining our non-significant pooled result and high heterogeneity. GCL and IPL thinning in ASD found in our analysis are supported by some prior reports suggesting inner retinal involvement. Compared to studies in adults with these conditions, the patterns might differ, with adult ADHD studies also yielding mixed results regarding RNFL and adult ASD studies sometimes suggesting more pronounced or different patterns compared to pediatric findings. This underscores the importance of considering age and developmental stage, as retinal structure changes throughout life, and the impact of neurodevelopmental conditions might evolve over time or interact with aging processes.[18-20]

5. Conclusion

This systematic review and meta-analysis synthesized data from seven studies to investigate retinal structural differences, as measured by OCT, between children and adolescents (≤18 years)

diagnosed with ADHD or ASD and typically developing controls. The pooled analyses revealed several key findings, children and adolescents with ADHD exhibited statistically significant thinning of the global average RNFL and GCL compared to typically developing controls, while children and adolescents with ASD showed statistically significant thinning of the GCL and IPL compared to typically developing controls. A trend towards global RNFL thinning was observed in ASD but did not reach statistical significance, and no significant differences in average macular thickness (or CST) were found for either ADHD or ASD groups compared to controls. Furthermore, moderate statistical heterogeneity was observed for most analyses where significant differences were found, suggesting variability across the included studies. The observed thinning of the inner retinal layers in children with ADHD and ASD aligns with the broader neurodevelopmental hypotheses for these disorders and the established eye-brain connection.

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