Normative Reference Ranges for the Retinal Nerve Fiber Layer, Macula, and Retinal Layer Thicknesses in Children

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• PURPOSE: To establish a normative database of peripapillary retinal nerve fiber layer (RNFL) thickness, macular thickness, and retinal layer thickness in healthy North American children, using spectral-domain optical coherence tomography (SD OCT).

• DESIGN: Prospective cross-sectional study.

• METHODS: This institutional study enrolled 83 healthy children (aged 5-15 years) as volunteer research subjects at the Retina Foundation of the Southwest (Dallas, Texas); all had normal visual acuity. Imaging was accomplished with the Spectralis SD OCT. Peripapillary RNFL thickness and macular thickness were assessed for 1 eye of each child using the Heidelberg Spectralis SD OCT software. Thicknesses of individual retinal layers and layer combinations were assessed using custom software to segment the line scans obtained with the Spectralis SD OCT.

• RESULTS: Average global peripapillary RNFL thickness was 107.6 ± 1.2 μm and average central subfield macular thickness was 271.2 ± 2.0 μm. Peripapillary RNFL thickness was thicker than has been reported in adults, particularly the superior and inferior sectors, and central subfield macular thickness was significantly correlated with age. While the thickness of most retinal layers was comparable with those of adults, the outer segment layer was 36% thinner in children than in adults.

• CONCLUSIONS: SD OCT can be used to assess peripapillary RNFL thickness, macular thickness, and retinal layer thickness in children as young as 5 years. Pediatric means and normative reference ranges are provided for each measurement. The values presented herein can be used as a standard with which to compare those of children suspected of having retinal or optic nerve abnormalities. (Am J Ophthalmol 2013;155: 354–360. © 2013 by Elsevier Inc. All rights reserved.)

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OPTICAL COHERENCE TOMOGRAPHY (OCT) IS A noncontact medical imaging technology similar to x-ray imaging and magnetic resonance imaging (MRI). Simply stated, OCT uses reflected light to produce a detailed, cross-sectional image of the eye. Image capture is noninvasive, fast, and painless.

Time-domain (TD) OCT was first used in 1991 to visualize the eye.[1] Although useful, images obtained using TD-OCT were 2-dimensional, image acquisition time was slow, and the axial resolution of the devices prohibited detailed analyses of retinal structure. In 2004, spectral-domain (SD) OCT (also commonly referred to as Fourier-domain [FD] OCT) entered clinical practice.[2] The generation of 3-dimensional images, increased speed of image acquisition, and increased axial resolution are 3 of the major advancements seen in the SD OCT devices used today. Having axial resolution between 1 and 5 μm, the newest SD OCT devices provide detailed measurements of the retinal nerve fiber layer (RNFL) and the macula. The images obtained from the newest SD OCT devices are of sufficient resolution to permit segmentation and measurement of individual retinal layers using computer-assisted programs.

Quantitative SD OCT is increasingly being used to detect eye disease, monitor changes in the progression of eye disease, and assess the efficacy of current and novel treatments for eye diseases in pediatric patients. For adult patients, SD OCT devices routinely compare the results obtained to a normative reference range, allowing for automatic detection of abnormalities. Unfortunately, as is the case with the Spectralis SD OCT (Heidelberg Engineering, Vista, California, USA) used in this study, the norms provided by SD OCT devices are for individuals 18 years of age and older. There are no internal standards with which to compare the results obtained in children.

Recently, Turk and associates used the Spectralis SD OCT to assess macular thickness, macular volume, and RNFL thickness in a cohort of 107 6- to 16-year-old Turkish children.[3] We want to expand upon this study in 2 ways: (1) we want to compile a normative database of North American children, including children of more diverse racial and ethnic backgrounds; and (2) we want to provide reference ranges for retinal layer thicknesses from the SD OCT images in order to broaden the scope of the normative database. Normative data for individual

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retinal layers segmented in SD OCT images may be useful in the differential diagnosis and management of vitreoretinal dystrophies and optic nerve disease, and can be useful in guiding molecular genetic testing.

METHODS

THIS PROSPECTIVE CROSS-SECTIONAL STUDY AND DATA accumulation were approved by the Institutional Review Board of the University of Texas Southwestern Medical Center (Dallas, Texas, USA). All data were collected at the Retina Foundation of the Southwest (Dallas, Texas, USA). Informed consent to participate in the research study was obtained from a parent or legal guardian. Assent was obtained from subjects between the ages of 10 and 15 years. The Retina Foundation of the Southwest complies with HIPAA regulations.

• **SUBJECTS:** A total of 83 healthy North American children (aged 5-15 years) were enrolled in this study. All children were seen at the Retina Foundation of the Southwest in Dallas, Texas. Children were included in this study if they were born at term (≥ 37 weeks postconception) and had best-corrected visual acuity of −0.10 to 0.20 logMAR, normal stereoacuity, no ocular abnormalities, no developmental delay, and no family history of retinal or optic nerve diseases or glaucoma. Of the 83 children, 45 were male and 38 were female; 3 were 5 years old, 10 were 6 years old, 13 were 7 years old, 12 were 8 years old, 13 were 9 years old, 6 were 10 years old, 10 were 11 years old, 6 were 12 years old, 4 were 13 years old, 4 were 14 years old, and 2 were 15 years old; 57 were non-Hispanic white, 5 were African American, 7 were Hispanic, 6 were Asian, 6 were more than 1 race/ethnicity, and 2 were not reported.

• **SPECTRAL-DOMAIN OCT IMAGING:** SD OCT imaging was accomplished with the Spectralis SD OCT (Heidelberg Engineering), using the automatic real-time (ART) eye tracker to eliminate motion artifacts. All children had pupil sizes larger than 3 mm, precluding the need for dilation. For each child, 3-5 high-resolution horizontal line scans (9 mm) and 2-3 high-density volume scans (5.9 × 4.4 mm or 8.6 × 7.2 mm, composed of 19 or 31 B-scans, respectively) were obtained from the macular region of the right eye. Based on quality scores, 1 9-mm horizontal foveal scan image and 1 volume scan image were chosen for analysis. Quality scores for scans are assigned by the Spectralis and expressed as a signal-to-noise ratio (SNR) in decibels (dB). Scans above 20 dB are considered high-quality. The average SNR value for the line scans reported in this manuscript were 33.5 ± 5.9 dB (mean ± standard deviation). The average SNR value for the volume scans reported in this manuscript was 29.6 ± 7.3 dB.

Results obtained from the high-speed volume scans of the macula were classified by region, as shown in Figure 1. The retinal thickness map was used to determine the numeric averages of thickness for 5 subfields within the Early Treatment Diabetic Retinopathy Study grid.[4] Because some of the children had volume scans that did not fill the entire template, we determined the average thickness within the 1-mm-diameter central foveal subfield (CFS) and the average thicknesses within the nasal, temporal, superior, and inferior segments of the 3-mm-diameter annulus.

Two or 3 high-speed peripapillary RNFL circle scans (circle scan size: 3.5 mm) were also obtained. Based on quality (average SNR values were 29.8 ± 6.9 dB), 1 RNFL image was chosen for analysis. The peripapillary RNFL thickness measurements (μm) were automatically calculated by the Spectralis SD OCT, and provided a global average (G) and the average thickness for each of 6 sectors (Figure 2): temporal (T), temporal-superior (TS), temporal-inferior (TI), nasal (N), nasal-superior (NS), nasal-inferior (NI).

• **RETINAL SEGMENTATION:** High-resolution horizontal line scans were segmented using a custom-designed program built in IGOR Pro (IGOR Pro 6.12; WaveMetrics Inc, Lake Oswego, Oregon, USA). This program was used to profile and measure the thickness of individual retinal layers and layer combinations (Figure 3).[5–7] The segmentation approach is comparable to the software developed by Hood and associates (MATLAB based; MathWorks, Natick, Massachusetts, USA).[8] The following layer and layer combination thicknesses were measured: total retinal thickness (TR), retinal nerve fiber layer (RNFL), retinal ganglion cell layer (RGC)+ (GCL + inner plexiform layer), inner nuclear layer (INL), outer nuclear layer (ONL), photoreceptor inner segments (IS), photoreceptor outer segments (OS), retinal pigment epithelium + Bruch membrane (RPE), OS+ (OS + RPE), and receptors (REC)+ (outer plexiform layer + ONL + IS + OS + RPE). Layer thicknesses from the segmented images were sampled at the center of the fovea (foveola) and at ±2 mm from the center of the fovea (outside the rim of the foveal pit).

Two individuals (S.E.Y., C.S.P.) independently marked retinal layer boundaries after a training period during which they discussed the boundaries of a sample set of scans with an experienced segmenter (Y.W.). It has been shown that after a training period, between-segmenter reliability is quite good.[9] The mean (range) of the concordance correlation coefficients for each retinal segmentation measurement was 0.9967 (0.9957-0.9975). The results of the 2 graders were averaged.

• **STATISTICAL ANALYSIS:** Statistical analyses were performed using MedCalc Software version 12.2.1 (Medcalc, Mariakerke, Belgium). Two-way analysis of

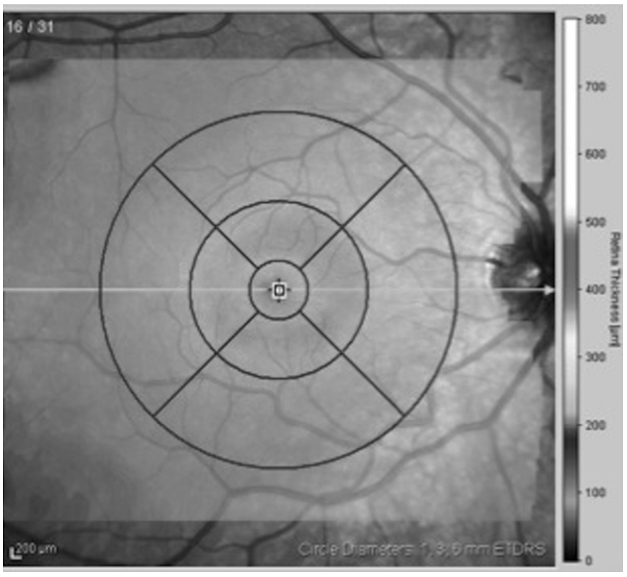

FIGURE 1. Early Treatment Diabetic Retinopathy Study subfield template[4] used to derive macular thickness measurements from different regions of a high-density volume scan of the macula. Circles are 1, 3, and 6 mm in diameter.

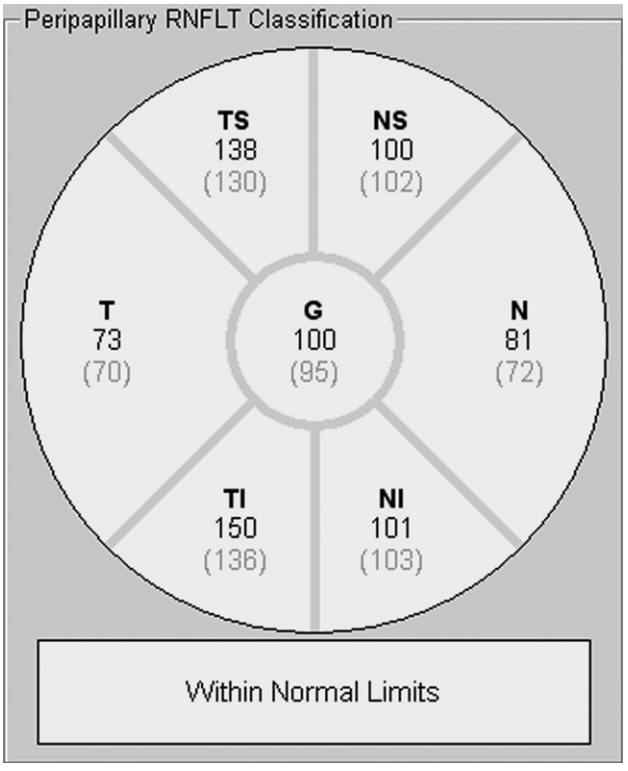

FIGURE 2. Sample retinal nerve fiber layer report provided by the Spectralis device for a retinal nerve fiber layer scan. Numbers directly under each sector name are the individual's mean retinal nerve fiber layer thickness (μm). Numbers in parentheses are the mean thickness of adults in the Spectralis normative database.[17,18]

variance (ANOVA) was used to examine the effects of sex and race/ethnicity (non-Hispanic white vs other race/ethnicity) on measured thicknesses. The effect of age on measured thicknesses was assessed using linear regression.

RESULTS

• **MACULAR THICKNESS:** The average macular thickness values for the 1-mm-diameter central foveal subfield and for each segment of the 3-mm-diameter circle are shown in Table 1. There were no significant effects of sex ($P = .134$) or race/ethnicity ($P = .177$) on central foveal subfield thickness. However, linear regression analysis demonstrated a significant increase in central foveal subfield thickness with age ($P = .032$; Figure 4).

• **PERIPAPILLARY RNFL THICKNESS:** The average peripapillary RNFL thickness values for each sector of the circular scan are shown in Table 2. Peripapillary RNFL thickness was greatest in the superior and inferior segments and thinner in the nasal and temporal segments. There were no significant effects of sex ($P = .951$) or race/ethnicity ($P = .053$) on global peripapillary RNFL thickness. Linear regression analysis failed to demonstrate any change in global peripapillary RNFL thickness by age ($P = .702$).

• **RETINAL LAYER THICKNESS:** Table 3 summarizes the segmented retinal layer thicknesses at the foveola and ±2 mm from the foveal center. There were no significant effects of sex ($P = .808$) or race/ethnicity ($P = .458$) on total retinal thickness at the fovea. Linear regression analysis failed to demonstrate any change in total retinal thickness at the foveola by age ($P = .413$). Both outer segment and inner segment layers were significantly thicker in the fovea than at ±2 mm from the foveal center ($P < .0001$ and $P < .001$, respectively). As expected, inner retinal layers were not measurable at the fovea and the RNFL was thicker in the nasal than in the temporal retina.

• **NORMATIVE REFERENCE RANGES:** For each of the thickness parameters, data normality was assessed using the Kolmogorov-Smirnov test. All parameters were normally distributed. Normative ranges of each parameter were constructed for children aged 5-15 years by determining the values corresponding to the fifth/95th and first/99th percentiles (Table 4). Values that lie within the range of the fifth through 95th percentiles may be considered normal. Those that lie outside of this range but within the first through 99th percentiles may be considered borderline. Values that lie beyond the first or 99th percentile may be considered abnormal.

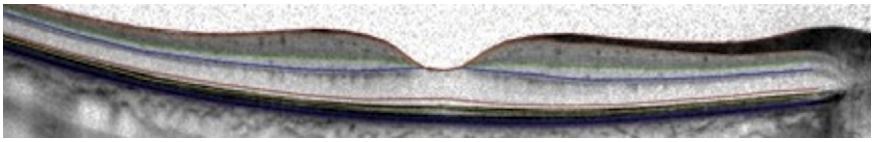

FIGURE 3. Representative Spectralis line scan image segmented using the IGOR segmentation program. Following manual segmentation, the program provides thickness measurements for each of 10 retinal layers or layer combinations (see text for additional details).

TABLE 1. Macular Thickness Measures in Normal Children[a]

Circle Diameter	Sector	All (n = 83)	Male (n = 45)	Female (n = 38)	NHW (n = 57)	Other[b] (n = 26)
1 mm	CSF	271.2 (2.0)	274.1 (2.5)	267 (3.3)	274.1 (2.3)	263.1 (3.8)
3 mm	N	334.9 (2.2)	340.4 (2.1)	326.8 (3.9)	335.3 (2.6)	332.0 (4.0)
	T	331.8 (1.7)	335. 9 (1.8)	326.0 (2.9)	331.3 (1.7)	331.9 (4.2)
	S	346.6 (1.7)	349.3 (1.8)	342.8 (3.0)	345.6 (1.8)	348.7 (3.9)
	I	333.4 (2.1)	338.4 (2.1)	326.2 (3.8)	334.0 (2.2)	330.3 (5.1)

CSF = central subfield; I = inferior; N = nasal; NHW = non-Hispanic white; S = superior; T = temporal.
[a]Values (μm) are means (± SEM).
[b]Other = black, Hispanic, Asian, and individuals of more than 1 race.

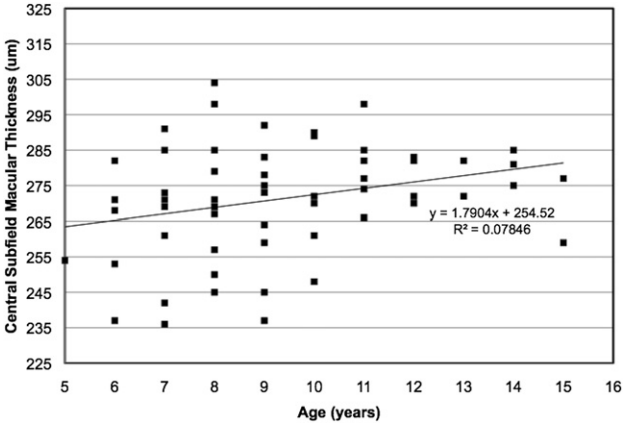

FIGURE 4. The relationship between age and 1-mm-diameter central subfield macular thickness in 83 normal children, aged 5-15 years. Central subfield macular thickness was measured using the Spectralis optical coherence tomography device, using the Early Treatment Diabetic Retinopathy Study subfield template.[4] A significant increase in central subfield macular thickness was found with increasing age (Pearson r = 0.28; $P = .032$).

DISCUSSION

SD OCT IS INCREASINGLY BEING USED AS A DIAGNOSTIC and monitoring tool in children with visual loss. Because of short exposure durations and eye-tracking systems in devices such as the Heidelberg Spectralis, quality images (with SNRs >20 dB) can be obtained in over 95% of children aged 5 years or older. Scans of the central retina are useful for identifying, monitoring, and classifying children with genetic retinal diseases such as Leber congenital amaurosis, retinitis pigmentosa, and Stargardt disease, or with abnormal retinal development such as in retinopathy of prematurity. Peripapillary RNFL scans can be useful for the detection and monitoring of glaucoma, optic nerve hypoplasia, and optic neuritis. However, for the scans to be the most useful for detecting diseases in children, quantitative measures from children should be compared to age-matched normal controls. Normal values from children are not currently available from manufacturers, and there is only a single normative study of Turkish children[3] available in the literature. The present study establishes a normative pediatric database for macular thickness, peripapillary RNFL thickness, and retinal layer thicknesses in healthy North American children using the Spectralis SD OCT.

Strengths of this study included a large cohort of healthy North American children with diverse racial and ethnic backgrounds, and the use of a current SD OCT technology with reproducible thickness measurements when used to test normal control adults and adult patients with degenerative retinal diseases.[7,10–13] One limitation of our study is that axial length was not measured; however, axial length has minimal influence on macular and RNFL thickness measurements.[3,14] Morisbakk and associates showed that scan-depth settings with Spectralis SD OCT have no effect on measured central foveal thickness in eyes with axial lengths that are within the range of the default setting (Morisbakk TL, et al. IOVS 2011;52:ARVO E-Abstract

TABLE 2. Peripapillary Retinal Nerve Fiber Layer Thickness Measures in Normal Children[a]

Sector	All (n = 83)	Male (n = 45)	Female (n = 38)	NHW (n = 57)	Other[b] (n = 26)
Global	107.6 (1.2)	107.7 (1.6)	107.4 (1.7)	105.3 (1.4)	112.9 (2.0)
T	76.5 (1.9)	76.1 (2.8)	77.0 (2.6)	74.2 (1.9)	84.7 (3.5)
TS	145.1 (2.2)	146.5 (2.9)	143.5 (3.2)	141.8 (2.5)	152.5 (4.0)
TI	147.0 (2.1)	145.2 (2.9)	149.0 (3.2)	142.2 (2.1)	157.6 (4.8)
N	84.5 (1.9)	84.9 (2.9)	84.1 (2.3)	84.8 (2.1)	84.1 (4.2)
NS	116.2 (2.8)	117.7 (3.4)	114.5 (4.5)	114.5 (3.1)	121.0 (6.1)
NI	125.4 (3.0)	124.7 (4.4)	126.2 (4.0)	122.2 (3.5)	131.6 (5.7)

G = global average; N = nasal; NHW = non-Hispanic white; NI = nasal-inferior; NS = nasal-superior; T = temporal; TI = temporal-inferior; TS = temporal-superior.

[a]Values (μm) are means (± SEM).

[b]Other = black, Hispanic, Asian, and individuals of more than 1 race.

TABLE 3. Retinal Layer Thicknesses in Normal Children[a]

Layer[b]	Center of Fovea[c]	2 mm Nasal	2 mm Temporal
TR	219.6 (1.7)	329.2 (2.3)	298.3 (1.9)
RNFL	–	35.6 (0.7)	14.5 (0.5)
RGC+	–	84.6 (0.9)	79.7 (0.7)
INL	–	45.0 (1.5)	41.3 (1.5)
ONL	–	91.2 (1.2)	89.8 (1.1)
IS	32.5 (0.5)	24.9 (0.5)	24.3 (0.5)
OS	44.3 (0.9)	28.1 (0.6)	28.5 (0.6)
RPE	22.5 (0.6)	21.8 (0.5)	21.7 (0.5)
OS+	66.9 (0.8)	49.8 (0.5)	50.1 (0.4)
REC+	210.2 (2.4)	164.0 (1.9)	162.9 (1.9)

[a]Values (μm) are means (± SEM).

[b]The following layers, or layer combinations, were measured: total retinal thickness (TR); retinal nerve fiber layer (RNFL); retinal ganglion cell layer + inner plexiform layer (RGC+); inner nuclear layer (INL); outer nuclear layer (ONL); photoreceptor inner segments (IS); photoreceptor outer segments (OS); retinal pigment epithelium + Bruch membrane (RPE); OS + RPE (OS+); and receptors + outer plexiform layer + ONL + IS + OS + RPE (REC+).

[c]Values for the RNFL, RGC+, and INL are denoted by dashes because of their absence at the center of the fovea. ONL values are similarly denoted by dashes because of the confounding inclusion of Henle fibers in ONL thickness measurement at the center of the fovea.

4048). Our cohort had normal distance visual acuity, so it is unlikely that they had significant myopia and increased axial length. Another limitation is that, although there was racial and ethnic diversity, our sample size was not sufficient to evaluate differences among each racial and ethnic group beyond comparing non-Hispanic white children to the other racial/ethnic groups taken together.

The average macular thickness (central subfield thickness) among all children aged 5-15 years of age was 271.2 ± 2.0 μm. This value is similar to that reported previously for Turkish children aged 6-16 years[3] and comparable to the data from healthy adults obtained with Spectralis SD OCT.[10,15] Despite the overall similarity to adult values, there was a significant increase in macular thickness between ages 5 and 15 years, with central subfield thickness averaging 10 μm less in children aged 5-7 years than in children aged 11-15 years. This trend is consistent with anatomic studies suggesting continued development of the fovea beyond the age of 5 years.[16,17] Unlike the study of children in Turkey,[3] no significant sex differences in central subfield thickness were found, although we did see a similar trend (male subjects having a thicker CSF than female).

The mean peripapillary RNFL thickness in children aged 5-15 years was 107.6 ± 1.2 μm, which is significantly higher than normative data for healthy white adults (18-78 years old) included in the Spectralis software.[18,19] Furthermore, the thicker RNFL in children is consistent with the significant negative correlation reported previously in adults between RNFL thickness and age.[18,20] Increased thickness relative to the Spectralis norms was most evident in the inferior and superior sectors, consistent with continued development of the maculopapular bundle beyond the age of 5 years.

The thicknesses of individual layers of the macula were measured with a manually assisted computer segmentation program. Segmentation values at the foveola reflected the characteristic displacement of inner retinal layers; the RNFL, RGC+, INL, and OPL were minimally detectable. The ONL-Henle fiber layer and RPE layer thicknesses were comparable to those of adults. The outer segment (OS) layer was 36% thinner in children than it is in adults,[8] consistent with the report that outer segments of 4-year-old children are 30%-50% shorter than those of adults.[17] Segmentation at ±2 mm eccentricity (beyond the foveal rim) demonstrated thickness values in children comparable to those of adults, a thicker RNFL nasally than temporally, and shorter OS compared with the OS at the foveola. In this study, sex did not affect total retinal thickness values.

TABLE 4. Normative Reference Ranges for Macular Thickness, Retinal Nerve Fiber Layer Thickness, and Retinal Layer Thicknesses in Children[a]

Circle Diameter		Mean (SEM)	5th Percentile	95th Percentile	1st Percentile	99th Percentile
1 mm	CSF	271.2 (2.0)	239.3	295.3	236.1	303.5
3 mm	N	334.9 (2.2)	308.1	357.7	283.3	368.4
	T	331.8 (1.7)	310.4	353.1	300.2	361.3
	S	346.6 (1.7)	323.5	366.6	323.0	380.9
	I	333.4 (2.1)	302.0	358.0	295.0	370.8
RNFL	Global	107.6 (1.2)	91.0	127.3	83.5	136.1
	T	76.5 (1.9)	58.1	104.3	21.3	137.1
	TS	145.1 (2.2)	112.6	179.6	99.5	198.9
	TI	147.0 (2.1)	115.6	184.9	108.3	194.5
	N	84.5 (1.9)	66.6	113.0	39.3	132.6
	NS	116.2 (2.8)	78.1	156.3	66.5	194.9
	NI	125.4 (3.0)	82.0	174.9	67.0	183.5
Retinal layer	TR	219.6 (1.7)	196.7	250.2	187.2	261.7
(fovea)[b]	RNFL	–	–	–	–	–
	RGC+	–	–	–	–	–
	INL	–	–	–	–	–
	ONL	–	–	–	–	–
	IS	32.5 (0.5)	25.5	39.9	19.4	43.1
	OS	44.3 (0.9)	30.4	59.4	23.1	62.2
	RPE	22.5 (0.6)	13.8	32.2	9.6	36.5
	OS+	66.9 (0.8)	56.1	79.6	48.8	83.4
	REC+	210.2 (2.4)	187.6	232.4	87.9	247.0

CSF = central subfield; G = global average; I = inferior; INL = inner nuclear layer; IS = photoreceptor inner segments; N = nasal; NI = nasal-inferior; NS = nasal-superior; ONL = outer nuclear layer; OS = photoreceptor outer segments; OS+ = OS + RPE; REC+ = outer plexiform layer + ONL + IS + OS + RPE; RGC+ = GCL + IPL; RNFL = retinal nerve fiber layer; RPE = retinal pigment epithelium + Bruch membrane; S = superior; T = temporal; TI = temporal-inferior; TR = total retinal thickness; TS = temporal-superior.

[a]Values (μm) are means (± SEM).

[b]Values for the RNFL, RGC+, and INL are denoted by dashes because of their absence at the center of the fovea. ONL values are similarly denoted by dashes because of the confounding inclusion of Henle fibers in ONL thickness measurement at the center of the fovea.

SD OCT may be especially useful for children with glaucoma or retinal diseases because it provides high-resolution, objective, quantitative assessments of the retinal layers affected by various diseases. The normative reference ranges for each of the SD OCT parameters for children aged 5-15 years enhance our ability to diagnose pediatric disorders affecting the retina and optic nerve, and provide guidance for molecular testing.[21–24]

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Biosketch

Susan E. Yanni, PhD, received her BS in neuroscience from the College of William and Mary in 2004. In 2010, she earned her PhD in Cell and Developmental Biology from Vanderbilt University. Following graduate school, Dr Yanni accepted a post-doctoral fellowship at the Retina Foundation of the Southwest (RFSW), Dallas, Texas. At the RFSW, her research focus has been two-fold: 1) retinopathy of prematurity, and 2) testing novel pediatric vision screening devices.