Normative Database of Optical Coherence Tomography Parameters in Childhood

Valores de Referência da Tomografia de Coerência Óptica na Idade Pediátrica

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ABSTRACT

Introduction: Optical coherence tomography is a technology that allows obtaining high resolution images of tissues in vivo, enabling the measurement of ocular structures, including the retinal nerve fiber layer and macular thickness. As a noninvasive test it's particularly useful in children, but its applicability is limited by the existence of normative values for adults only.

Purpose: To establish the pediatric normative values of retinal nerve fiber layer thickness and macular thickness and to investigate its relationship with sex, age, refraction, eye side and ocular dominance.

Material and Methods: Ophthalmologic examination and Cirrus HD-optical coherence tomography (Carl Zeiss Meditec) were carried out on 153 children aged 4 to 17 years old.

Results: We obtained a mean retinal nerve fiber layer average thickness of 97.90 µm. No significant differences were detected between genders, however the eye side and ocular dominance had significant influence on retinal nerve fiber layer thickness. Retinal nerve fiber layer thickness increased significantly with more positive refraction. With the Macular Cube 512 x 128 protocol we found that the average central subfield showed the smallest thickness (250.35 µm) and boys had higher macular thickness.

Discussion: The values of the retinal nerve fiber layer thickness and macular thickness obtained are comparable to recent studies. The distribution of retinal nerve fiber layer thickness in quadrants is in agreement with the normal distribution of retinal nerve fiber layer. Macular thickness proved to be higher in males (center field and inner ring), data consistent with previous studies.

Conclusion: We establish the normative retinal nerve fiber layer thickness and macular thickness in healthy Portuguese children. These data enhance the evaluation and interpretation of parameters obtained by optical coherence tomography in the diagnosis of pediatric disorders in clinical practice.

Keywords: Child; Macula Lutea; Nerve Fibers; Retina; Tomography, Optical Coherence.

RESUMO

Introdução: A tomografia de coerência óptica é um exame que permite obter imagens de alta resolução dos tecidos in vivo, possibilitando a medição das estruturas oculares, nomeadamente a camada de fibras nervosas da retina e a espessura macular. Como método não invasivo torna-se particularmente útil em crianças, contudo a sua aplicabilidade está limitada pela existência de valores normativos apenas para adultos.

Objetivo: Estabelecer na idade pediátrica valores normativos para a espessura da camada de fibras nervosas da retina e espessura macular, averiguando a sua influência com o género, idade, refração, lateralidade e dominância ocular.

Material e Métodos: Foram submetidas a exame oftalmológico e a Cirrus HD-tomografia de coerência óptica (Carl Zeiss Meditec) 153 crianças dos quatro aos 17 anos.

Resultados: Obtiveram-se valores da espessura média global da camada de fibras nervosas da retina de 97,90 µm. Não se detectaram diferenças entre géneros e com a idade, mas sim consoante a lateralidade e dominância ocular. Verificou-se um aumento da espessura com refrações positivas. Com o protocolo Macular Cube 512 x 128 verificou-se que o campo central apresentou a menor espessura (250,35 µm), apresentando os rapazes maior espessura macular.

Discussão: Os valores da espessura da camada de fibras nervosas da retina e da espessura macular obtidos são comparáveis a estudos recentes. A distribuição da espessura por quadrantes respeita a distribuição normal da camada de fibras nervosas da retina. A espessura macular revelou-se superior no género masculino (campo central e anel interno), dados estes também concordantes com estudos prévios.

Conclusão: Estabelecemos as normativas da espessura da camada de fibras nervosas da retina e espessura macular em crianças portuguesas saudáveis, dados estes que reestruturam a avaliação e interpretação dos parâmetros obtidos pela tomografia de coerência óptica no diagnóstico de patologias pediátricas na prática clínica.

Palavras-chave: Criança; Fibras Nervosas; Macula Lutea; Retina; Tomografia de Coerência Óptica.

INTRODUCTION

Optical coherence tomography (OCT), initially described by Huang *et al.* in 1991, is a medical imaging technique that uses low-coherence interferometry to determine echo-time and magnitude of light reflectivity on objects.[1] High-resolution (3 to 15 µm) 3D images are therefore obtained, allowing for in vivo measurement of optic structures, including the cornea, retina, retinal nerve fibre layer (RNFL), macula and the optic disc.[2] For all these reasons, OCT emerged to the forefront of ocular imaging technology and is currently a major diagnostic and follow-up procedure in optic neuropathies, retinal pathologies and abnormalities of the optic nerve, macular oedema and macular hole, among others.[2-5]

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New-generation OCT, the spectral-domain OCT (SD-OCT), allows for better resolution, better quality and shorter time of image acquisition (40 to 110 times faster than the previous model – the time-domain OCT), with fewer motion artifacts.[2,4,6]

As a non-invasive, quick and innocuous method with no direct ocular contact, OCT is particularly useful in children[7,8] and its feasibility and reproducibility is already established in this population.[8-10] However, its applicability in paediatric age is limited as there are only standard values for people aged over 18. Data regarding standards in children are scarce in the literature[3,5,7,8,10-14] and even fewer regarding the use of SD-OCT.[4,14-17] As far as it was possible for us to assess, there are no publications regarding both RNFL and macular thickness obtained by SD-OCT in Caucasian children between 4 and 17 years of age.

As such, our study aimed to determine RNFL and macular thickness standards in healthy Portuguese children, as well as to determine the influence of patient's gender, age, ocular refraction, laterality and dominance upon these parameters.

MATERIAL AND METHODS

Population

This was an observational, cross-sectional and analytical study carried out at the Ophthalmology Department of the Hospital of Braga over six consecutive months, authorised by the Director of the Ophthalmology Department and the Hospital's Ethics Committee. The agreement to participate in the study was made through the child's verbal consent and signed informed consent by the legal responsible.

Our group of patients included Caucasian children aged 4 to 17 attending to the Ophthalmology Clinic and meeting the inclusion criteria namely with monocular corrected visual acuity of at least 10/10 and spherical equivalent (SE) refractive error between -5 and +5 dioptres. The exclusion criteria were the following: prematurity; history or evidence of amblyopia or strabismus; family history of glaucoma; optic disc abnormalities suggesting the presence of glaucoma (cup-to-disc ratio ≥ 0.5 in any eye; ratio asymmetry between both eyes ≥ 0.2; haemorrhage) or any other abnormality observed by direct ophthalmoscopy or with slit lamp; previous ophthalmic surgery; previous ocular trauma and delayed psychomotor development.

All eligible children underwent ophthalmic examination including an orthoptic evaluation, a slit lamp biomicroscopy and non-dilated pupil fundoscopy. Best-corrected visual acuity was determined for each child using the Snellen chart, with and without optic correction, when necessary. Refractive errors were assessed under subjective refraction measured with auto-refractometer (Topcon KR-8900). Cyclopegia was induced with cyclopentholate hydrochloride 10mg/ml (three drops in total every five minutes), in non-cooperative children or when judged necessary. Refractive error was measured at least 40 minutes following the last drop. For the analysis, the refractive error was recorded as SE and calculated as follows: SE = sphere + cylinder/2. The identification of the dominant eye was based on the Dolman test (hole-in-card test).[18] Data regarding participant's gender, age, family and personal history were obtained from the electronic clinical records.

SD-OCT

RNFL and macular thickness were obtained with the SD-OCT (Cirrus HD-OCT, *model* 4000; Carl Zeiss Meditec). These procedures were carried out with no pupil dilation as optical and image acquisition speed in this model allow quality images to be obtained from a pupil diameter of 2.5 mm.[19] All procedures were performed by the same person (TQ) and using the same device; three measurements for each protocol on each eye were obtained, the average of which was recorded for the present study.

The Optic Disc Cube 200x200 scan protocol was used to determine the RNFL thickness (global average thickness, thickness by quadrant - superior, temporal, inferior and nasal – and individual thickness for twelve 30º sectors) and the Macular Cube 512x128 protocol was used to assess macular thickness and volume. The average thickness was obtained across nine sectors formed by three circles with 1 mm, 3 mmm and 6 mm in diameter, divided into four quadrants, namely superior, nasal, inferior and temporal. Except for the central circle, all these areas were obtained with this protocol.[19]

A display of an internal fixation target ensured a centralized scan through direct observation of the fundus on the screen. These were used on both protocols and in every patient in the study. Images with a signal strength < 5, poorly centred, with motion artefacts or incomplete were excluded from the study.

Statistical analysis

This was carried out using Statistical Package for the Social Sciences version 20 software (IBM SPSS Statistics v.20.0). Data normalization was checked with the Kolmogorov-Smirnov test and the skewness and kurtosis measures and subsequent descriptive statistics were carried out in order to characterise the sample. Central and dispersion tendency measures were obtained and percentile 99, 95, 5 and 1 were defined for all the parameters obtained by the OCT. Variables between the right and the left eye were compared, as well as between the dominant and non-dominant eye, using the paired sample t-test, between genders using the independent sample t-test, RNFL *vs.* macular regions were compared

between quadrants using Bonferroni-corrected repeated measures through ANOVA, in order to identify which pair averages were significantly different. Finally, multiple linear regression was used to allow for the estimation of RNFL and macular thickness (dependent variables) according to gender, age and refractive error (independent variables).

The results are shown as mean ± standard deviation (SD) and a statistical significance was considered for *p*-values ≤ 0.05 (95% confidence interval).

RESULTS

Characteristics of our group of patients

In total, 164 children underwent the OCT, from whom 11 were subsequently excluded from the analysis due to poor quality images. As such, our group included 306 eyes from 153 children (82 female – 53.6%), aged on average 9.54 ± 3.35, without any statistically significant differences between gender and average age (p = 0.310). Ocular dominance, identified in all children, was predominantly assigned to the right eye (59.5%). The average SE in our group of patients was -0.39 ± 1.33 dioptres, without any statistically significant difference between genders (p = 0.242), ocular laterality and dominance (p = 0.937).

RNFL thickness was obtained in 140 children (91.5%) and macular thickness in 152 children (99.3%).In some younger children the optic disc protocol was not obtained and in one child the opposite occurred.

Analysis of RNFL thickness

Global average RNFL thickness per quadrant and for each of the 12 sectors obtained in the OCT are shown in Table 1. Global average RNFL thickness in all the eyes was 97.90 ± 9.32 µm, with relevant and statistically significant differences observed between quadrants (p < 0.001). In fact, the average values of the inferior (129.58 ± 15.05 µm) and superior quadrant RNFL thickness (126.91 ± 16,51 µm) were higher than nasal (69.72 ± 10.47 µm) and temporal quadrant RNFL thickness (65.17 ± 8.91 µm) (all the p < 0.05). No statistically significant differences between the first two quadrants were found (p = 0.238), whilst these were found between nasal and temporal quadrants (p < 0.001), the latter showing the lowest thickness.

As regards RNFL thickness gender distribution, we should mention that no statistically significant differences were found (Table 2). RNFL thickness distribution according to the ocular laterality and dominance (Table 2) revealed that the left eye showed higher thickness at the superior quadrant compared to the right eye (p = 0.0055) whilst a higher thickness was found at the temporal quadrant of the right eye (p < 0.001). We also found that the dominant eye showed higher RNFL thickness at the temporal quadrant, compared to the non-dominant eye (p = 0.0145).

The multiple linear regression analysis (Table 3) allowed for the identification of SE as a significant predictor of global average RNFL (β = 0.218; p = 0.011), superior (β = 0.217; p = 0.012) and inferior quadrant thickness (β = 0.203; p = 0.018). This variable showed a positive correlation with these RNFL parameters with an increasing RNFL thickness with positive refractions. We found an average 1.6 µm, 2.8 µm and 2.4 µm increase in global average, superior and inferior quadrant thickness, respectively, for each positive SE dioptre. Child's gender and age did not show any

Table 1 – Distribution of RNFL thickness parameters obtained in 140 children (280 eyes)

RNFL thickness (µm)	Mean (DP)	P99	P95	P5	P1
Global average	97.90 (9.32)	124.34	112.00	83.08	73.55
SQ	126.91 (16.51)	186.72	156.42	104.53	85.26
IQ	129.58 (15.05)	166.75	156.40	104.53	95.28
TQ	65.17 (8.91)	88.95	79.48	50.50	47.71
NQ	69.72 (10.47)	98.59	91.30	54.03	48.41
Sector 1	118.62 (20.04)	169.63	150.00	90.00	67.88
Sector 2	85.56 (16.89)	135.27	118.92	60.58	54.21
Sector 3	52.97 (8.65)	76.30	69.87	40.05	35.23
Sector 4	68.08 (12.82)	97.77	93.92	46.55	42.91
Sector 5	108.86 (20.96)	170.17	145.50	76.03	67.91
Sector 6	143.70 (22.73)	202.30	181.90	109.53	86.71
Sector 7	136.34 (21.55)	184.84	171.35	101.03	87.35
Sector 8	68.61 (12.85)	107.65	92.98	50.10	42.73
Sector 9	50.25 (6.17)	66.89	60.50	40.03	37.62
Sector 10	76.59 (12.51)	118.86	95.00	59.03	53.00
Sector 11	130.48 (22.44)	203.51	168.37	93.00	79.41
Sector 12	131.68 (26.76)	212.89	181.17	91.03	65.56

RNFL, retinal nerve fibre layer; SD, standard deviation; P, percentile; IQ, inferior quadrant; NQ, nasal quadrant; SQ, superior quadrant; TQ, temporal quadrant.

Table 2 - Comparison of the different RNFL thickness parameters between male vs. female; left vs. right eye and dominant vs. non-dominant eye

RNFL thickness (µm)	Mean (SD)		p	Mean (SD)		p	Mean (SD)		p
	Male (n=65)	Female (n=75)		Left eye	Right eye		Dominant eye	Non-dominant eye	
Média global	96.79 (9.63)	98.87 (8.99)	0.190	97.53 (9.60)	98.28 (9.61)	0.061	97.96 (9.70)	97.85 (9.51)	0.0791
QS	126.14 (17.41)	127.57 (15.76)	0.610	128.39 (18.03)	125.43 (17.67)	0.0055	126.62 (17.62)	127.19 (18.19)	0.627
QI	127.65 (16.18)	131.25 (13.897)	0.158	129.71 (16.09)	129.44 (16.01)	0.774	129.46 (16.42)	129.69 (15.69)	0.809
QT	65.51 (9.39)	64.88 (8.53)	0.679	62.91 (8.73)	67.44 (10.48)	<0.001	66.09 (9.55)	64.43 (10.09)	0.0145
QN	68.02 (9.33)	71.20 (11.22)	0.073	69.16 (11.78)	70.28 (10.98)	0.143	69.41 (11.01)	70.03 (11.77)	0.421

RNFL, retinal nerve fibre layer; SD, standard deviation; P, percentile; IQ, inferior quadrant; NQ, nasal quadrant; SQ, superior quadrant; TQ, temporal quadrant

significant effect on thickness prediction of any of the RNFL parameters obtained in the OCT.

Macular thickness analysis

Macular global average thickness, central field and each of the four quadrants, as well as total macular volume obtained by the OCT are shown in Table 4. Relevant and statistically significant differences were found between the different macular areas ($p < 0.001$) and the lowest thickness was found in the central field (250.35 ± 19.28 µm), followed by the outer ring average thickness (279.91 ± 12.16 µm). In turn, the highest macular thickness was found in the inner ring (316.03 ± 14.05 µm) and this tendency remained when comparing the correspondent quadrants (all $p < 0.05$). In addition, when thickness was compared between the quadrants from the same ring, the following ascending order was found: temporal <inferior <superior <nasal quadrant (all $p < 0.05$). These are relevant and statistically significant differences both in macular inner ($p < 0.001$) and outer regions ($p < 0.001$).

As shown in Table 5 male patients had statistically significant higher macular thickness at the central field ($p = 0.0135$) and the inner ring, both regarding the global average ($p = 0.01$), for the inferior ($p = 0.015$), temporal ($p = 0.001$) and nasal quadrants ($p = 0.0125$). As for RNFL, we found that the left eye showed higher thickness at the superior quadrant of the macular outer ring, compared to the right eye ($p = 0.024$). The temporal quadrant showed higher thickness in the right eye as well, both in macular inner ($p = 0.0025$) and outer rings ($p = 0.0115$) (Table 5). As regards the distribution of macular thickness according to macular dominance, we did not find any statistically significant differences on any of the assessed parameters (Table 5).

The multiple linear regression analysis (Table 6) showed that child's gender ($\beta = -0.214$; $p = 0.006$), age ($\beta = 0.187$; $p = 0.019$) and SE ($\beta = -0.204$; $p = 0.011$) were significant predictors of central field macular thickness. We found an average 8 µm reduction in thickness in female gender and this was the independent variable with the highest relative contribution. SE also showed a negative correlation with the central field thickness and a reduction in thickness was found with positive refractions (on average 3 µm reduction per positive dioptre in SE). Child's age, on the other hand, showed a positive correlation with this parameter and an average 1 µm annual increase in thickness was found. Gender is also a significant predictor of global macular thickness in the inner ring ($\beta = -0.204$; $p = 0.012$) and temporal ($\beta = -0.268$; $p = 0.001$) and nasal correspondent quadrants ($\beta = -0.204$; $p = 0.012$). A negative correlation with these parameters of macular thickness was also found. An average 5.7, 7.6 and 6 µm reduction in global average

Table 3 - Results of multiple linear regression with the different RNFL thickness parameters as dependent variables

RNFL thickness (µm)	IV	F (3.136)	B	beta (β)	CI UL	CI LL	p	R^2_{AJ}
Global average	Gender	4.176; p = 0.007	2.262	0.122	5.284	-0.761	0.141	0.064
	Age		-0.331	-0.115	0.147	-0.808	0.174	
	SE		1.587	0.218	2.801	0.373	0.011	
QS	Gender	3.136; p = 0.015	1.766	0.054	7.154	-3.621	0.518	0.053
	Age		-0.587	-0.116	0.264	-1.439	0.175	
	SE		2.800	0.217	4.964	0.636	0.012	
QI	Gender	3.709; p = 0.013	3.884	0.129	8.792	-1.024	0.120	0.055
	Age		-0.474	-0.103	0.300	-1.252	0.227	
	SE		2.396	0.203	4.367	0.425	0.018	
QT	Gender	0.660; p = 0.578	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	
QN	Gender	1.961; p = 0.123	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	

---- non-significant adjusted model ($p > 0.05$)

RNFL, retinal nerve fibre layer; SE, spherical equivalent; CI, confidence interval; UL, upper limit; LL, lower limit; IQ, inferior quadrant; NQ, nasal quadrant; SQ, superior quadrant; TQ, temporal quadrant; IV, independent variables.

Table 4 - Distribution of macular thickness and volume parameters assessed from 152 children (304 eyes)

Macular Thickness (µm)	Mean (SD)	P99	P95	P5	P1
Global MT	282.26 (11.59)	314.05	300.35	263.13	258.00
CF	250.35 (19.28)	292.03	283.70	217.80	207.83
Inner Ring					
Superior	320.31 (14.36)	353.91	347.18	295.50	289.77
Inferior	316.55 (14.38)	347.71	341.18	293.50	283.27
Temporal	305.87 (14.15)	338.91	330.50	282.33	283.27
Nasal	321.38 (14.99)	357.94	348.50	299.33	290.27
Outer Ring					
Superior	283.25 (13.18)	322.72	306.50	261.15	252.56
Inferior	273.01 (14.40)	323.21	295.20	249.98	243.77
Temporal	263.09 (12.34)	298.97	283.68	244.50	240.77
Nasal	300.29 (14.33)	332.82	322.50	274.98	259.98
Volume (mm^3)					
Total volume	10.17 (0.41)	11.31	10.82	9.47	9.28

CF, central field; SD, standard deviation; MT, macular thickness; P, percentile.

thickness in the inner ring and in their correspondent temporal and nasal quadrants, respectively, was found in female patients. We also found that child's age is a significant predictor of macular thickness at the superior quadrant of the outer ring ($\beta = -0.177$; $p = 0.033$), negatively correlated to this parameter. No significant influence of any of the independent variables (gender, age, SE) was found in the remaining macular thickness parameters.

DISCUSSION

The OCT has been shown to be particularly useful in paediatric age, allowing for a diagnosis and follow-up of optical neuropathies, retinal pathologies, optic nerve abnormalities and even intracranial.[15,20,21] It became a feasible procedure in this population,[7,10,14] supported by our study, where quality images were obtained in 93.3% of our patients. Its applicability is still limited in current clinical practice by the lack of standards for children.

Most available literature regarding standard values for

Table 5 - Comparison of the different macular thickness and volume parameters between male vs. female; left vs. right eye and dominant vs. non-dominant eye

Macular Thickness (µm)	Mean (SD)		p	Mean (SD)		p	Mean (SD)		p
	Male (n=65)	Female (n=75)		Left eye	Right eye		Dominant eye	Non-dominant eye	
Global MT	281.82 (12.09)	282.64 (11.20)	O.666	282.17 (11.99)	282.36 (11.66)	O.631	282.22 (11.82)	282.31 (11.84)	0.810
CF	254.07 (17.61)	247.17 (20.16)	0.0135	250.55 (19.57)	250.15 (19.44)	0.415	250.37 (19.35)	250.30 (19.74)	0.893
Inner ring									
Global average	318.89 (14.29)	313.59 (13.44)	0.01	315.87 (14.65)	316.19 (14.06)	0.515	316.19 (14.16)	315.88 (14.56)	0.525
SQ	322.18 (15.24)	318.71 (13.45)	0.138	320.48 (15.17)	320.14 (14.53)	0.582	320.66 (14.38)	319.95 (15.31)	0.252
IQ	319.29 (14.38)	314.21 (14.04)	0.015	316.07 (15.87)	317.03 (13.98)	0.149	316.57 (14.47)	316.43 (15.29)	0.852
TQ	309.76 (13.92)	302.55 (13.57)	0.001	305.16 (14.62)	306.58 (14.35)	0.0025	305.74 (14.12)	302.63 (14.62)	0.859
NQ	324.33 (15.34)	318.87 (14.30)	0.0125	321.78 (15.24)	320.99 (15.29)	0.093	321.41 (15.28)	321.35 (15.26)	0.889
Outer ring									
Global average	278.92 (13.12)	280.76 (11.29)	0.362	279.95 (12.47)	279.87 (12.41)	0.850	279.88 (12.46)	279.96 (12.39)	0.862
SQ	281.26 (13.39)	284.95 (12.84)	0.085	283.95 (13.82)	282.54 (13.95)	0.024	282.86 (13.66)	283.64 (14.14)	0.276
IQ	271.24 (14.79)	274.52 (13.97)	0.163	272.49 (15.46)	273.53 (14.73)	0.156	273.14 (15.34)	272.88 (14.87)	0.716
TQ	264.21 (13.77)	262.12 (10.98)	0.308	262.57 (12.59)	263.61 (12.72)	0.0115	263.46 (12.54)	262.71 (12.78)	0.102
NQ	298.98 (15.71)	301.40 (13.02)	0.307	300.78 (14.80)	299.79 (14.55)	0.056	300.05 (15.02)	300.531 (14.34)	0.357
Volume (mm^3)									
Total volume	10.15 (0.44)	10.19 (0.40)	0.597	10.17 (0.43)	10.17 (0.42)	0.670	10.17 (0.43)	10.17 (0.43)	0.887

RNFL, retinal nerve fibre layer; SD, standard deviation; CF, central field; IQ, inferior quadrant; NQ, nasal quadrant; SQ, superior quadrant; TQ, temporal quadrant.

OCT in children refers to other OCT models that, due to different image acquisition and axial resolution algorithms, make measurements non interchangeable.[22-24] More recently, Barrio-Barrio *et al.*, and Al-Haddad *et al.* described RNFL and macular thickness standards using Cirrus OCT in Caucasian children. Our study complements these as it describes other RNFL thickness parameters, namely the thickness per each of 12 individual sectors, as well as the distribution of RNFL and macular thickness according to ocular laterality and dominance.

The values for RNFL thickness in the 140 children involved in our study are in line with the recent studies that used Cirrus OCT.[9,15-17] Thickness distribution by quadrant (inferior> superior> nasal> temporal), previously described in children,[3,9,10,14-17] meets the normal RNFL distribution around the optic nerve, also known as the ISNT rule or double-hump configuration. This configuration is due to the higher number of nerve fibres converging to the optic nerve head from the superior and inferior arcade when compared to the number of fibres converging from the papillomacular bundle and nasal retina.[3] The RNFL asymmetry according to laterality has been shown, in line with previous studies in children[8,25] and in adults,[1,26] where the left eye showed higher thickness at the superior quadrant and the right eye showed higher thickness in the temporal quadrant, although the underlying physiological mechanism remains to be determined. Ocular dominance, predominantly assigned to the right eye, in line with literature,[18] had an influence on the results, with higher RNFL thickness in the temporal quadrant of the dominant eye. Other references describing this correlation by quadrants were not found and therefore further studies will be needed in order to confirm these results. The influence of the refractive error is questionable and some studies did not find any correlation[27,28] whilst others,[3,8,10,16,17] in line with ours, found a reduction in RNFL thickness with negative refractions. There is no consensual explanation for this fact and it has been proposed that the real diameter of the circular scan in a myopic eye (with longer axial length) is higher than the pre-defined diameter, reducing the measure of RNFL thickness.[29] This may represent a measurement artefact and not a real structural abnormality. Regardless of the explanation, as OCT is an optic method, it is possible that the refractive error might affect OCT measurements, providing the rationale for excluding children with SE > ±5 dioptres from the study. Differences regarding RNFL parameters according to gender were not found, in line with most studies[10,14-17] and this variable did not show any significant effect on thickness prediction. Similarly, child's age did not show any significant effect, in line with literature.[4,7,10,12,14-17] The results found were acceptable (a significant reduction in RNFL thickness is only observed above the age of 50)[15] and were in line with studies carried out in adults with Cirrus OCT.[22] This non-linear reduction with child's age and the narrow age group of children in the different studies may explain for the lack of association that was found between these parameters and therefore further longitudinal studies are needed in order to clarify this issue.

Macular thickness was studied in a larger number of children, its protocol facilitated by the tendency of young children to look at a target located at the centre of the fovea. The values of macular thickness from the 152 children involved in our study are in line with the studies that used Cirrus OCT.[9,16,17,30] Topographically and in line with other references,[5,11,13,16,17] the inner ring showed the highest macular thickness and, when compared by quadrant, the temporal showed the lowest thickness in both regions. In line with previous studies,[5,11,13,16,17,31] macular thickness distribution by quadrants within the outer ring (temporal< inferior< superior< nasal) is consistent with the convergence of the retinal nerve fibres at the optic disc. Macular thickness showed to be higher in male gender in the central field and the inner ring, but not in the outer ring, in line with previous studies in children [4,5,11,16,17] and in adults.[31,32] This may be explained by the retinal layers external to the RNFL, which represent most of the macular thickness in these regions.[31] Nevertheless, the layer responsible for this difference has not yet been identified. There was no impact of child's gender on macular thickness. The impact of gender on macular thickness was also shown in multiple linear regression analysis where this variable has been shown as the strongest predictor in the central field. The distribution of macular thickness according to laterality showed differences consistent with those found for RNFL, namely higher macular thickness in the outer superior quadrant in the left eye and in the inner and outer temporal quadrant in the right eye. Only one study with the time-domain OCT in 6-year-old children found this asymmetry and obtained a similar result only in the superior quadrant.[25] Age differences and OCT versions used may explain for the different results found. Differences were not found in any of the parameters according to ocular dominance. Samarawickrama *et al.* only studied the differences at the central field and likewise failed to find asymmetry.[33] Using multiple linear regression, we found an increase in macular thickness in the central field with negative refractions, in line with previous studies in children[5] and in adults.[34,35] Wu *et al.* proposed that the tendency to the lengthening and flattening of the internal limiting membrane (ILM) would lead to foveal elevation and consequently higher thickness.[35] The fact that this is an avascular anatomical region makes it more prone to distortion, supporting the abovementioned hypothesis.[5] These data should be carefully considered, as the study by Wu *et al.* only involved patients with SE > -6

Table 6 - Results of multiple linear regression with the different macular thickness and volume parameters as dependent variables

Macular Thickness (µm)	IV	F (3.136)	B	β	CI UL	CI LL	p	R^2_{AJ}
Global MT	**Gender**	0.421; $p = 0.739$	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	
CF	**Gender**	7.057; $p < 0.001$	-8.241	-0.214	-2.346	-14.137	0.006	0.107
	Age		1.074	0.187	1.972	0.176	0.019	
	SE		-2.955	-0.204	-0.687	-5.224	0.011	
Inner Ring								
Global average	**Gender**	2.947; $p = 0.035$	-5.735	-0.204	-1.274	-10.195	0.012	0.037
	Age		0.496	0.119	1.176	-0.184	0.151	
	SE		-0.638	- 0.060	1.078	-2.355	0.464	
Superior	**Gender**	1.794; $p = 0.151$	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	
Inferior	**Gender**	2.291; $p = 0.081$	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	
Temporal	**Gender**	4.188; $p = 0.007$	-7.571	-0.268	-3.129	-12.012	0.001	0.060
	Age		0.354	0.084	1.031	-0.322	0.302	
	SE		-0.678	-0.064	1.031	-2.387	0.434	
Nasal	**Gender**	3.704; $p = 0.013$	-6.105	-0.204	-1.378	-10.832	0.012	0.051
	Age		0.629	0.141	1.350	-0.091	0.086	
	SE		-1.156	-0.103	0.663	-2.975	0.211	
Outer Ring								
Global average	**Gender**	1.377; $p = 0.252$	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	
Superior	**Gender**	2.874; $p = 0.038$	4.179	0.159	8.368	-0.010	0.051	0.036
	Age		-0.693	-0.177	-0.055	-1.331	0.033	
	SE		0.376	0.038	1.988	-1.236	0.645	
Inferior	**Gender**	1.653; $p = 0.180$	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	
Temporal	**Gender**	2.211; $p = 0.089$	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	
Nasal	**Gender**	0.881; $p = 0.453$	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	
Volume (mm^3)								
Total volume	**Gender**	0.473; $p = 0.702$	----	----	----	----	----	----
	Age		----	----	----	----	----	
	SE		----	----	----	----	----	

---- Non-significant adjusted model ($p > 0.05$)

RNFL, retinal nerve fibre layer; CF, central field; MT, macular thickness; SE, spherical equivalent; CI, confidence interval; UL, upper limit; LL, lower limit; IV, independent variables.

dioptres, the different studies are not consensual[4,11,16,17] and the precise mechanism underlying this relationship is still unclear. Patient's age has also shown a negative influence and an increase in central field's macular thickness has been found with age, in line with previous studies,[11,14,16,17] consistent with anatomical studies suggesting foveal continuous development upon the age of 5.[14]

It should be mentioned that other variables show their influence on the parameters obtained in the OCT. The patient's ethnic origin is one of the factors largely studied and with a recognized impact on RNFL[15,36] and macular thickness.[11,36] As our study did not include children from other ethnic origins, the results should be carefully considered. In addition, the normative in adults generally include perimetry assessment, gonioscopy and axial length measurement. Even though it has been recognized that the influence of axial length in Caucasian children is reduced,[15] we opted not to include assessments that may be difficult to perform in this age group, in order to avoid restricting study participation. Other possible limitations include the dimension of the sample and the fact that all children were recruited from an outpatient clinical setting and therefore our group of patients may not accurately reflect general paediatric population. Strict inclusion and exclusion criteria were established in order to minimize this bias. Further studies with larger samples, stratified by age group, gender and ethnic origin, as well as clarifying the influence of other variables on RNFL and macular thickness will contribute to progress in the field.

CONCLUSION

This is the first study that establishes the normative regarding RNFL and macular thickness in Portuguese healthy children aged 4 to 17 using the Cirrus SD-OCT. This information has the potential to rebuild the assessment and interpretation of the parameters obtained with the OCT for the diagnosis of paediatric pathologies in clinical practice, in which child's gender, ethnic origin and refractive error should be carefully considered.

CONFLICT OF INTERESTS

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