COMPARISON OF RETINAL NERVE FIBER LAYER AND MACULAR THICKNESS IN MALAY CHILDREN WITH AND WITHOUT STRABISMUS

BY

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Introduction: Optical coherence tomography (OCT) has been widely used globally to study the retinal nerve fiber layer thickness (RNFLT) and macular thickness (MT) in patients with strabismus and strabismic amblyopia of different ethnicities. There are o similar published literature found involving patients of Malay ethinicity.

Objectives: To compare the mean RNFLT and MT between Malay children with and without strabismus and strabismic Malay children with and without amblyopia.

Patients and Methods: A prospective, comparative cross sectional study was conducted in Ophthalmology Clinic, Hospital Universiti Sains Malaysia from February 2012 to January 2014. A total of 136 Malay children aged 3 to 16 years were recruited for this study; 68 each in strabismus and without stabismus (normal) group. Strabismic children were subgrouped into 17 in strabismus with amblyopia and 51 in strabismus without amblyopia group. A comprehensive ocular examination which included orthoptic assessment, cycloplegic refraction, intraocular pressure measurement, anterior segment and dilated fundus

examination was performed. The mean RNFLT and MT were measured using the Cirrus HD-OCT.

Results: The mean average RNFLT in Malay children with strabismus [97.04(11.99) μm] was significantly thinner as compared to normal Malay children [101.10(9.04) μm], p = 0.02. The superior quadrant RNFLT was also significantly thinner in the strabismus group as compared to normal group (p = 0.041). The mean average MT was 277.23(15.53) μm and 282.38(10.46) μm in the strabismus and normal groups, respectively, reaching statistically significant difference (p = 0.025). The means of superior outer MT (p = 0.049), superior inner MT (p = 0.019), inferior inner MT (p = 0.028) and nasal inner MT (p = 0.023) were significantly thinner in Malay children with strabismus as compared to normal Malay children. There were no significant differences of mean RNFLT and MT between strabismic Malay children with and without amblyopia (p > 0.05).

Conclusion: Malay children with strabismus have thinner RNFLT and MT than normal orthophoric Malay children. The mean RNFLT and MT are comparable between strabismic Malay children with and without amblyopia.

Associate Professor Dr Shatriah Ismail: Supervisor

DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.

Date : 27th November 2014

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Alisa Victoria Koh

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ABBREVIATIONS

AMO	Alternating monocular occlusion
BCVA	Best corrected visual acuity
COV	Coefficient of variation
CV	Coefficient of variance
D	Dioptre
GCC	Ganglion cell complex
HD-OCT	High-definition optical coherence tomography
ICC	Intraclass correlation coefficient
ISNT	Inferior-superior-nasal-temporal
LGN	Lateral geniculate nucleus
logMAR	Logarithm of the Minimum Angle of Resolution
MT	Macular thickness
NF1	Neurofibromatosis type 1
OCT	Optical coherence tomography
OPGs	Optic pathway gliomas
RNFLT	retinal nerve fiber layer thickness
SE	Spherical equivalent
SP	Spherical power retinal
SD-OCT	Spectral-domain optical coherence tomography
TD-OCT	Time-domain optical coherence tomography
TMR	Total macular retinal

ABSTRAK

Pengenalan: Mesin tomografi kepaduan optik telah digunakan secara global untuk mengkaji ketebalan lapisan saraf retina dan ketebalan macula di kalangan pesakit berbilang etnik yang mempunyai masalah mata juling dan mata malas yang disebabkan oleh mata juling. Setakat ini, tiada penerbitan artikel berkenaan kajian yang serupa yang melibatkan pesakit berbangsa Melayu.

Objektif: Membanding purata ketebalan lapisan saraf retina dan macula di antara kanak-kanak Melayu yang mempunyai masalah mata juling dengan kanak-kanak Melayu tanpa masalah mata juling (normal) dan di antara kanak-kanak bermasalah mata juling yang bermata malas dan tidak bermata malas.

Metodologi: Kajian perbandingan keratin rentas ini telah dijalankan di Klinik Oftalmologi, Hospital Universiti Sains Malaysia dari Februari 2012 sehingga Januari 2014. Seramai 136 kanak- kanak Melayu berumur antara 3 dan 16 tahun telah dipilih untuk menyertai kajian ini; 68 dalam kumpulan masalah mata juling dan 68 dalam kumpulan tanpa mata juling (normal). Kanak-kanak bermasalah mata juling dibahagikan kepada 17 yang bermata malas dan 51 yang tidak bermata malas. Pemeriksaan mata yang teliti termasuk pemeriksaan ortoptik, pemeriksaan refraksi mata, pengukuran tekanan bebola mata, pemerikaan struktur bahagian hadapan mata dan pemeriksaan fundus mata. Ketebalan lapisan saraf retina dan makula diukur menggunakan mesin tomografi kepaduan optik Cirrus HD-OCT.

Keputusan: Purata ketebalan lapisan saraf retina pada kanak-kanak Melayu bermasalah mata juling [97.04 (11.99) μm] adalah lebih nipis berbanding dengan kanak-kanak tanpa masalah mata juling [101.10 (9.04) μm], p =0.027. Ketebalan lapisan saraf retina superior juga ketara lebih nipis dalam kumpulan bermasalah mata juling ini berbanding kumpulan normal (p = 0.041). Purata ketebalan macula ialah 277.23 (15.53) μm dan kumpulan tanpa masalah mata juling, mencapai perbezaan statistic yang signifikan (p = 0.025). Purata ketebalan macula luar superior (p = 0.049), ketebalan macula dalam superior (p = 0.019), ketebalan macula dalam inferior (p = 0.028) dan ketebalan macula dalam nasal (p = 0.023) adalah lebih nipis pada kanak-kanak Melayu bermasalah mata juling berbanding kanak-kanak normal. Tidak ada perbezaan yang signifikan diperhatikan untuk purata ketebalan lapisan saraf retina dan macula antara kanak-kanak Melayu bermasalah mata juling yang bermata malas dengan yang tanpa mata malas (p>0.05).

Kesimpulan: Kanak-kanak Melayu bermasalah mata juling mempunyai ketebalan lapisan saraf retina dan ketebalan macula yang lebih nipis berbanding kanak-kanak Melayu tanpa masalah mata juling. Ketebalan lapisan saraf retina dan ketebalan macula adalah setandng antara kanak-kanak Melayu bermasalah mata juling yang bermata malas dan yang tanpa mata malas.

ABSTRACT

Introduction: Optical coherence tomography (OCT) has been widely used globally to study the retinal nerve fiber layer thickness (RNFLT) and macular thickness (MT) in patients with strabismus and strabismic amblyopia of different ethnicities. There are o similar published literature found involving patients of Malay ethinicity.

Objective: To compare the mean RNFLT and MT between Malay children with and without strabismus and strabismic Malay children with and without amblyopia.

Methodology: A prospective, comparative cross sectional study was conducted in Ophthalmology Clinic, Hospital Universiti Sains Malaysia from February 2012 to January 2014. A total of 136 Malay children aged 3 to 16 years were recruited for this study; 68 each in strabismus and without stabismus (normal) group. Strabismic children were subgrouped into 17 in strabismus with amblyopia and 51 in strabismus without amblyopia group. A comprehensive ocular examination which included orthoptic assessment, cycloplegic refraction, intraocular pressure measurement, anterior segment and dilated fundus examination was performed. The mean RNFLT and MT were measured using the Cirrus HD-OCT.

Result: The mean average RNFLT in Malay children with strabismus [97.04(11.99) µm] was significantly thinner as compared to normal Malay children [101.10(9.04) µm], p = 0.02. The superior quadrant RNFLT was also significantly thinner in the strabismus group as compared to normal group (p = 0.041). The mean average MT was 277.23(15.53) µm and 282.38(10.46) µm in the strabismus and normal groups,

respectively, reaching statistically significant difference ($p = 0.025$). The means of superior outer MT ($p = 0.049$), superior inner MT ($p = 0.019$), inferior inner MT ($p = 0.028$) and nasal inner MT ($p = 0.023$) were significantly thinner in Malay children with strabismus as compared to normal Malay children. There were no significant differences of mean RNFLT and MT between strabismic Malay children with and without amblyopia ($p > 0.05$).

Conclusion: Malay children with strabismus have thinner RNFLT and MT than normal orthophoric Malay children. The mean RNFLT and MT are comparable between strabismic Malay children with and without amblyopia.

Table 4.4 Comparison of mean RNFLT

RNFLT (μm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p-value*
	Strabismus, N = 68	Control, N = 68			
Superior	122.75 (21.87)	129.88 (18.23)	7.13 (0.30, 13.96)	2.07 (134)	**0.041**
Inferior	127.06 (20.76)	131.22 (14.86)	4.16 (-1.97, 10.29)	1.34 (121)	0.181
Temporal	68.02 (11.39)	70.97 (9.16)	2.96 (-0.55, 6.46)	1.67 (134)	0.098
Nasal	70.29 (12.25)	72.24 (12.40)	1.94 (-2.24, 6.12)	0.92 (134)	0.360
Average	97.04 (11.99)	101.10 (9.04)	4.06 (0.46, 7.66)	2.23 (134)	**0.027**

* Independent t test was applied. p-value < 0.05 was considered statistically significant. SD= standard deviation, df = degree of

Table 4.5 Comparison of mean RNFLT

RNFLT (μm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p value*
	Exotropia, n = 40	Normal, n = 68			
Superior	119.50 (20.71)	129.88 (18.24)	-10.38 (-17.96, -2.80)	-2.72 (106)	0.080
Inferior	124.03 (20.26)	131.22 (14.86)	-7.20 (-14.54, 0.15)	-1.96 (64)	0.055
Temporal	66.35 (11.10)	70.97 (9.16)	-4.62 (-8.54, -0.70)	-2.34 (106)	**0.021**
Nasal	68.33 (11.55)	72.24 (12.40)	-3.91 (-8.69, 0.87)	-1.62 (106)	0.108
Average	94.58 (11.22)	101.10 (9.04)	-6.53 (-10.44, -2.62)	-3.31 (106)	**0.001**

* Independent t test was applied. SD= standard deviation, df = degree of freedom.

Table 4.6 Comparison of mean RNFLT

RNFLT (μm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p value*
	Esotropia, n = 28	Normal, n = 68			
Superior	127.39 (23.01)	129.88 (18.24)	-2.49 (-11.29, 6.31)	-0.56 (94)	0.575
Inferior	131.39 (21.06)	131.22 (14.86)	0.17 (-7.35, 7.70)	0.045 (94)	0.964
Temporal	70.93 (11.59)	70.97 (9.16)	-0.58 (-5.00, 3.84)	-0.26 (94)	0.796
Nasal	73.11 (12.87)	72.24 (12.40)	0.87 (-4.72, 6.46)	0.31 (94)	0.758
Average	100.57 (12.37)	101.10 (9.04)	-0.53 (-5.04, 3.98)	-0.23 (94)	0.815

* Independent t test was applied. SD= standard deviation, df = degree of freedom.

Table 4.7 Comparison of Mean RNFLT

RNFLT (μm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p value*
	Exotropia, n = 40	Esotropia, n = 28			
Superior	119.50 (20.71)	127.39 (23.01)	7.89 (-2.78,18.56)	1.477 (66)	0.144
Inferior	124.03 (20.26)	131.39 (21.06)	7.37 (-2.77,17.50)	1.452 (66)	0.151
Temporal	66.35 (11.10)	70.93 (11.59)	4.04 (-1.52,9.60)	1.452 (66)	0.151
Nasal	68.33 (11.55)	73.11 (12.87)	4.78 (-1.17,10.74)	1.603 (66)	0.114
Average	94.58 (11.22)	100.57 (12.37)	6.00 (0.24,11.75)	2.080 (66)	**0.041**

* Independent t test was applied. RNFLT= retinal nerve fiber layer thickness, SD= standard deviation, df = degree of freedom.

Table 4.8 Comparison of mean MT

MT (µm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p-value*
	Strabismus, N = 68	Normal, N = 68			
Outer macula					
Superior	282.62 (19.24)	288.47 (14.90)	5.85 (0.02, 11.69)	1.98 (134)	**0.049**
Inferior	272.44 (18.76)	272.06 (11.51)	-0.43 (-5.71, 4.86)	-0.16 (111)	0.873
Temporal	263.87 (17.75)	267.63 (11.61)	3.76 (-1.33, 8.86)	1.46 (115)	0.146
Nasal	299.06 (18.95)	302.77 (13.23)	3.71 (-1.84, 9.26)	1.32 (120)	0.189
Inner macula					
Superior	307.40 (24.31)	316.27 (18.65)	8.87 (1.51, 16.22)	2.39 (126)	**0.019**
Inferior	305.50 (25.07)	313.74 (17.26)	8.24 (0.93, 15.55)	2.23 (119)	**0.028**
Temporal	297.79 (22.53)	304.16 (18.15)	6.37 (-0.57, 13.30)	1.82 (128)	0.072
Nasal	312.49 (20.68)	319.54 (14.57)	7.05 (0.99, 13.13)	2.30 (120)	**0.023**
Central Macular Thickness	229.72 (23.57)	230.56 (20.39)	0.87 (-6.64, 8.31)	0.22 (134)	0.825
Average Macular Thickness	277.23 (15.53)	282.38 (10.46)	5.15 (0.66, 9.65)	2.27 (117)	**0.025**

*Independent t test was applied. p-value < 0.05 was considered statistically significant. SD= standard deviation, df= degree of freedom.

Table 4.9 Comparison of mean MT

MT (µm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p value*
	Exotropia, n = 40	Normal, n = 68			
Outer macula					
Superior	278.90 (18.24)	288.47 (14.90)	-9.57 (-15.97, -3.17)	-2.96 (106)	**0.004**
Inferior	272.00 (20.15)	272.02 (11.51)	-0.01 (-6.99, 6.96)	-0.01 (54)	0.997
Temporal	259.80 (16.02)	267.63 (11.61)	-7.83 (-13.62, -2.04)	-2.70 (63)	**0.009**
Nasal	298.60 (18.59)	302.77 (13.23)	-4.16 (-10.26, 1.93)	-1.36 (106)	0.178
Inner macula					
Superior	305.68 (20.10)	316.27 (18.65)	-10.59 (-18.17, -3.01)	-2.77 (106)	**0.007**
Inferior	303.25 (24.79)	313.74 (17.26)	-10.49 (-19.37, -1.60)	-2.36 (62)	**0.021**
Temporal	296.73 (20.02)	304.16 (18.15)	-7.44 (-14.89, 0.01)	-1.98 (106)	0.050
Nasal	310.25 (20.89)	319.54 (14.57)	-9.29 (-16.78, -1.81)	-2.48 (62)	**0.016**
Central Macular Thickness	227.55 (21.61)	230.56 (20.39)	-3.01 (-11.25, 5.23)	-0.72 (106)	0.471
Average Macular Thickness	275.05 (14.42)	282.38 (10.46)	-7.33 (-12.55, -2.12)	-2.81 (63)	**0.007**

*Independent t test was applied. SD= standard deviation, df= degree of freedom

Table 4.10 Comparison of mean MT

MT (µm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p value*
	Esotropia, n = 28	Normal, n = 68			
Outer macula					
Superior	287.93 (19.71)	288.47 (14.90)	-0.54 (-8.91, 7.82)	-0.13 (40)	0.896
Inferior	273.07 (16.91)	272.02 (11.51)	1.06 (-6.00, 8.12)	0.30 (38)	0.764
Temporal	269.68 (18.75)	267.63 (11.61)	2.05 (-5.69, 9.78)	0.54 (36)	0.595
Nasal	299.71 (19.78)	302.77 (13.23)	-3.05 (-11.29, 5.19)	-0.75 (37)	0.458
Inner macula					
Superior	309.86 (29.54)	316.27 (18.65)	-6.41 (-18.62, 5.81)	-1.06 (36)	0.294
Inferior	308.71 (25.59)	313.74 (17.26)	-5.02 (-13.94, 3.90)	-1.12 (94)	0.267
Temporal	299.32 (26.00)	304.16 (18.15)	-4.84 (-15.74, 6.06)	-0.90 (38)	0.374
Nasal	315.68 (20.33)	319.54 (14.57)	-3.87 (-12.42, 4.69)	-0.91 (39)	0.366
Central Macular Thickness	232.82 (26.22)	230.56 (20.39)	2.26 (-7.65, 12.17)	0.45 (94)	0.651
Average Macular Thickness	280.34 (16.77)	282.38 (10.46)	-2.04 (-8.97, 4.88)	-0.60 (36)	0.553

*Independent t test was applied. SD= standard deviation, df= degree of freedom

Table 4.11 Comparison of mean MT

MT (µm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p value*
	Exotropia, n = 40	Esotropia, n = 28			
Outer macula					
Superior	278.90 (18.24)	287.93 (19.71)	9.03 (-2.48, 18.30)	1.94 (66)	0.056
Inferior	272.00 (20.15)	273.07 (16.91)	4.18 (-8.76, 17.13)	0.23 (66)	0.819
Temporal	259.80 (16.02)	269.68 (18.75)	9.88 (1.42, 18.34)	2.33 (66)	**0.023**
Nasal	298.60 (18.59)	299.71 (19.78)	1.11 (-8.27, 10.50)	0.24 (66)	0.813
Inner macula					
Superior	305.68 (20.10)	309.86 (29.54)	4.18 (-8.76, 17.13)	0.65 (44)	0.518
Inferior	303.25 (24.79)	308.71 (25.59)	5.46 (-6.89, 17.82)	0.88 (66)	0.380
Temporal	296.73 (20.02)	299.32 (26.00)	2.60 (-8.55, 13.75)	0.47 (66)	0.643
Nasal	310.25 (20.89)	315.68 (20.33)	5.43 (-4.74, 15.59)	1.066 (66)	0.290
Central Macula Thickness	227.55 (21.61)	232.82 (26.22)	5.27 (-6.34, 16.88)	0.91 (66)	0.368
Average MacularThickness	275.05 (14.42)	280.34 (16.77)	5.29 (-2.30, 12.88)	1.39 (66)	0.169

*Independent t test was applied. SD= standard deviation, df= degree of freedom

Table 4.15 Comparison of mean RNFLT

RNFLT (μm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p-value*
	Amblyopia, N = 17	Non-amblyopia, N = 51			
Superior	130.41 (23.36)	120.20 (20.98)	-10.22 (-22.28, 1.85)	-1.69 (66)	0.096
Inferior	127.12 (19.49)	127.04 (21.35)	-0.08 (-11.77, 11.62)	-0.10 (66)	0.989
Temporal	65.41 (8.23)	68.88 (12.22)	3.47 (-2.89, 9.83)	1.09 (66)	0.280
Nasal	73.94 (8.33)	69.08 (13.15)	-4.86 (-11.66, 1.93)	-1.43 (66)	0.158
Average	99.18 (10.54)	96.33 (12.45)	-2.84 (-9.56, 3.88)	-0.85 (66)	0.401

* Independent t test was applied. p-value < 0.05 was considered statistically significant. SD= standard deviation, df = degree of freedom.

Table 4.16 Comparison of mean MT

MT (µm)	Mean (SD)		Mean difference (95% CI)	t statistics (df)	p value*
	Amblyopia, N = 17	No amblyopia, N=51			
Outer macula					
Superior	286.00 (18.23)	281.49 (19.61)	-4.51 (-15.29, 6.27)	-0.84 (66)	0.407
Inferior	269.65 (18.20)	273.37 (19.02)	3.73 (-6.80, 14.25)	0.71 (66)	0.482
Temporal	270.35 (20.17)	261.71 (16.52)	-8.65 (-18.42, 1.13)	-1.77 (66)	0.082
Nasal	297.18 (22.36)	299.69 (17.88)	2.51 (-8.15, 13.17)	0.47 (66)	0.640
Inner macula					
Superior	304.24 (32.85)	308.45 (21.03)	4.22 (-13.47, 21.90)	0.50 (21)	0.625
Inferior	305.35 (30.59)	305.55 (23.31)	0.20 (-13.93, 14.32)	0.03 (66)	0.978
Temporal	298.06 (27.38)	297.71 (20.98)	-0.35 (-13.04, 12.34)	-0.06 (66)	0.956
Nasal	311.18 (24.99)	312.92 (19.30)	1.75 (-9.90, 13.39)	0.30 (66)	0.766
Central Macular Thickness	231.00 (24.08)	229.30 (21.76)	-1.71 (-14.98, 11.57)	-0.26 (66)	0.798
Average Macular Thickness	277.56 (18.51)	277.12 (14.61)	-0.44 (-9.19, 8.30)	-0.10 (66)	0.920

* Independent t test was applied. p-value < 0.05 was considered statistically significant. SD= standard deviation, df = degree of freedom.

1.1 Strabismus

1.1.1 Prevalence of Strabismus

Strabismus is defined as misalignment of the eyes. It is a paediatric eye condition of which if left untreated would persist into adulthood. Few population-based studies have reported the prevalence of strabismus in children to be in the range of 0.01% to 3.3% globally. Studies from China and Japan reported a strabismus prevalence of 1.9% (He *et al*., 2004) and 0.01% (Matsuo *et al.,* 2007) respectively which was lower than strabismus prevalence in Mexico (2.3%) (Ohlsson *et al*., 2003), Australia (2.8%), (Robaei *et al*., 2006), United Kingdom (2.3%) (Williams *et al*., 2008) and United States (3.3%) (Friedman *et al*., 2009).

In the Baltimore Paediatric Eye Disease Study which was conducted in Baltimore, Maryland, United States, 2546 white and African American children aged 6 through 71 months were examined. The result revealed that 3.3% of white and 2.1% of African American children had manifest strabismus. This had brought to a total of about 677,000 cases of manifest strabismus among children 6–71 months of age in the United States (Friedman *et al*., 2009).

East Asian investigators had also reported on the prevalence of strabismus in children based on large-scale population-based studies (He *et al*., 2004; Matsuo and Matsuo, 2007; Yoon *et al*., 2011). Using questionnaires returned back from Japanese children aged 6 to 12 years old, 1112 (1.28%) of total 86531 children were found to have strabismus (Matsuo and Matsuo, 2007).

In Korea, Yoon *et al*. (2011) reported strabismus prevalence of 1.8% in children aged 3 to 5 years. He *et al*. (2004) whose study primarily focused on assessing visual impairment in Southern Chinese children aged 5 to 15 reported the prevalence of strabismus to be 1.9%.

Chia *et al*. (2010) reported a lower prevalence of strabismus (0.8%) among young Singaporean Chinese children. Their study included 3009 children aged 6 to 72 months. Majority of the strabismic children had esotropia (73.4%) while 21.4% had exotropia and 5.2% had hypertropia.

A Malaysian data showed the prevalence of strabismus in children to be at 2.2% (Teoh and Yow, 1982). Teoh and Yow (1982) conducted the study in an urban city of Petaling Jaya, involving 650 school children aged 7. Fourteen (2.2%) of them were found to have strabismus, of which 86% were exotropia, 7% alternating esotropia and 7% hypertropia.

In terms of types of strabismus, studies in Asian populations have shown an esotropia to exotropia ratio of less than 1, whereas in Caucasian populations, the ratio was greater than 1. This indicated that there are more exotropias among Asians but on contrary more esotropias among the Caucasians. Hyperopia was postulated to influence the distribution of strabismus (Cotter *et al*., 2011). Yu *et al*. (2002) reported a higher prevalence of exotropia in Hong Kong as the population becomes less hyperopic.

1.1.2 Risk Factors for Developing Strabismus

The onset of strabismus is generally found to be before the age of 5. Silbert *et al*. (2013) studied on the incidence of strabismus and amblyopia in preverbal children aged 2-33 months. They reported that these children previously diagnosed with pseudoesotropia had a significant risk of subsequently developing esotropia. Twelve percent of the pseudoesotropic children who returned for follow-up were found to have strabismus or mild refractive amblyopia. The authors observed that hyperopia of less than 1.50 dioptre (D) did not obviate the need for careful follow-up. This indicated that meticulous examination and regular follow up is important to detect strabismus to enable prompt treatment to be carried out.

Cosgrave *et al*. (2008) reported that low birth weight and premature birth are associated with development of strabismus. Infants with high-risk prethreshold retinopathy of prematurity (ROP) have been found to have increased rate of strabismus by VanderVeen *et al*. (2011). VanderVeen *et al*. (2011) examined 341 premature infants with high risk prethreshold ROP at 9 months corrected age and at 6 years old. The prevalence of strabismus was noted to be 42.2% at 6 years of age. The authors noted that unfavourable structural outcome due to ROP (4.93 times greater risk), abnormal fixation behaviour (5.28 times greater risk), history of amblyopia (2.91 times greater risk) and history of anisometropia ≥2 D (0.47 times greater risk) were the important associated factors of strabismus in these children.

Higher prevalence rate of strabismus was also reported with positive family history. Birch *et al*. (2005) reported that in 86 children with strabismus, 22% had parents or siblings with strabismus. On the other hand, 77% of the 86 accomodative esotropic children had strabismic parent, sibling, grandparents, aunt or uncle. However the authors noted that not all children with a positive family history of strabismus should be candidates for intervention.

1.1.3 Impact of Strabismus

Strabismus affects these children emotionally, psychologically and socially apart from affecting their vision. This is due to its poor cosmetic appearance. Paysse *et al*. (2001) evaluated thirty-four naïve children between 3 and 7 years of age, each separately, a set of three identical dolls. The eyes were altered so that one was orthotropic, one esotropic, and one exotropic. Each child was given 10 minutes to play with the dolls. They were interviewed afterwards about their preferences towards the dolls. Children aged 5 years and older were found to express their dislikes towards strabismic dolls by throwing and verbally disparaging non orthotropic dolls. This was found to be 73 times more likely in these children than the younger children.

Mojon-Azzi *et al*. (2011) studied on the social acceptance of children with strabismus by their peers. They enrolled 118 Swiss children aged 3-12 years to determine the age at which strabismus impinged upon psychosocial interactions. The children were asked to select from photographs, one of the twins whom they would like to invite to their birthday party. Photographs of six children were digitally altered to create pictures of identical twins with different position of the eyes (orthotropic, exotropic and esotropic) and the colour of the shirt. Children younger than 6 years old did not make significant preference between strabismic and orthotropic children. Children aged 6 years or older who invited children with squint to their birthday parties were significantly lesser compared to orthotropic children. The authors noted gender, colour of the shirts or type of strabismus made no impact on the children likings. From the results of this study, they concluded that children age 6 years and above with visible squint are less favoured by their peers.

Lukman and Choong (2010) conducted a study in Malaysia which showed that even children age 5 had negative reactions toward their peers with strabismus. A total of 128 children age 5 to 6 years old were enrolled in this cross-sectional within-group study. The children viewed four paired images of peers with orthotropia and exotropia. They were told to choose the image they liked and the image they would share their favourite toy with. A greater proportion of children favoured the images that showed images of peer with orthotropia ($p < 0.001$). They concluded that children as young as 5 year old perceived strabismus in negative social reactions.

Lin *et al*. (2014) reported that the prevalence of alcohol use among strabismic Southern Chinese children aged 10 to 17 years was significantly higher than children without strabismus (62.3% versus 36.3%; $p < 0.01$). The study also revealed that strabismic children more likely to show positive screening responses for depression and anxiety than normal children. The negative effects noted in these studies further emphasize the importance of diagnosing and treating strabismus before it could cause psychological and emotional scar to these patients.

1.2 Strabismic Amblyopia

1.2.1 Prevalence of Strabismic Amblyopia

Strabismic amblyopia is less frequently found in Asian preschool children compared to refractive amblyopia. Lower level of strabismic amblyopia have been found in Singapore (15.0%), Korea (12.8%) and Taiwan (2.6%) (Lim *et al*., 2004; Chang *et al*., 2007; Chia *et al*., 2010). Preslan *et al.* (1996), Newman *et al.* (1996), Robaei *et al.* (2006) and Williams *et al.* (2008) reported higher prevalence of strabismic amblyopia in Caucasian children in United States, Australia and United Kingdom ranging from 26% to 44%. There is no data on the characteristics of types of amblyopia among Malaysian children.

The prevalence of strabismus among young Singaporean Chinese children aged 6 to 72 months was found to be 0.80% by Chia *et al*. (2010). Twelve point five percent of these children with strabismus had amblyopia, indicating strabismic amblyopia prevalence of 0.10%. This is almost six times lesser than the amblyopia caused by refractive errors.

A similar study conducted earlier by Friedman *et al*. (2009) reported manifest strabismus in 3.3% of White and 2.1% of African American children. Amblyopia was found in 10.0% of the strabismic children, which was similar to that of Singapore data (Chia *et al.,* 2010). Strabismic amblyopia affected 0.2% of African-Americans and 0.6% of white Americans. These data suggested that only one tenth of strabismus children have amblyopia.

The multicentre Pediatric Eye Disease Investigator Group reported almost equal proportions of patients with strabismic and anisometropic amblyopia. The researchers examined 409 children below 7 years old with moderate amblyopia. and reported the cause of amblyopia was strabismus in 38% while anisometropic amblyopia in 37%. Combined strabismic and anisometropia was the aetiology in 24% of the total patients (Pediatric Eye Disease Investigator Group, 2002).

1.2.2 Pathophysiology of Strabismic Amblyopia

Amblyopia is defined as unilateral or less commonly bilateral reduced best corrected visual acuity (BCVA) in the absence of organic abnormality of the eye (von Noorden, 1985). In strabismus, there is disruption of binocular vision which leads to images forming in non-corresponding points in both retinae. However, diplopia or confusion does not occur due to visual adaptation via anomalous retinal correspondence (Nelson, 1988) or suppression.

In strabismic amblyopia, the overlapping of different foveal images from the fixating and deviating eye causes active inhibition within the retinocortical pathways of visual input which originates from the fovea of the deviating eye (von Noorden, 1985). The author proposed that the aetiology of strabismic amblyopia is similar to suppression. However, they are not interchangeable as suppression is limited to binocular vision with normal monocular visual acuity but amblyopia exists under both monocular and binocular conditions. Hence, suppression cannot be the sole cause of amblyopia.

Fahle (1987) utilised the concept of binocular rivalry to measure binocular inhibition. The author observed that the high ratio of dominance in the ipsilateral visual field indicated that ipsilateral temporal visual field was more dominant than the weaker contralateral nasal visual field. Fahle (1987) suggested that this asymmetry observed might be related to the nasotemporal asymmetry of retinocortical projections. Through this observation, Fahle (1987) proposed that amblyopia occurs more commonly in esotropia due to competition of the strabismic eye's fovea with the

strong temporal hemifield of the contralateral eye. Contrarily, in exotropia, it competes with the much weaker nasal hemifield.

Sengpiel and Blakemore (1994) hypothesised that orientation-dependent interocular suppression may underlie the psychophysical phenomenon of binocular rivalry. They investigated on strabismic monkeys in which strabismus were surgically induced by lateral rectus myotomy, and observed non orientation specific suppression. All cells showing clear suppression in the primary visual cortex were located in layers 4B, 4Ca and 6. Coincidently, the magnocellular layer of lateral geniculate nucleus also projects specifically to these layers. They proposed that the interocular suppression seen in monkey is more pronounce for the neurons of the magnocellular pathway which is thought to be more concerned with stereopsis than parvocellular pathway.

1.2.3 Animal Studies related to Strabismus and Amblyopia

Tremain and Ikeda (1982) studied the relationship between amblyopia and cortical ocular dominance in six cats which squint which were induced surgically. Five cats were reared as control and did not have ocular interference. The researchers measured the visual acuity of cells in lateral geniculate nucleus (LGN) receiving inputs from the area centralis. They determined the ocular dominance distribution of cells in area 17 of visual cortex. Cats with amblyopia showed a greater degree of apparent shrinkage of Nissl stained LGN cells and greater proportion of cortical cells excited by the control eye than by the experimental eye. Furthermore, the degree of amblyopia and shrinkage of the LGN cells were correlated with the degree of loss of binocular cells.

Earlier, Von Noorden created an animal model which mimics human strabismic amblyopia in macaque monkeys by operating on extraocular muscles during infancy (Von Noorden, 1970). In subsequent study, the author reported cell shrinkage in the layers of LGN that received input from amblyopic monkey eyes by histologic examination (Von Noorden, 1973). He observed that the findings in the LGN were similar in visual deprivation and strabismic amblyopia. He summarized that binocular competition at the LGN or cortical level occurred in both visual deprivation and strabismus and resulted in similar changes in the primate visual system.

These morphological changes in the layers of the binocular segment of the LGN that receive input from the deprived eye in animals were supported by a postmortem study in human amblyopic eye (Von Noorden and Crawford, 1983). Despite having shown histological abnormalities in LGN layers that receive input from the affected eye, the current consensus dictates that neural responses of both the retina (Cleland *et al*., 1980; Cleland *et al*., 1982) and LGN are normal (Levitt *et al*., 2001).

1.3 Optical coherence tomography (OCT)

Researches in ophthalmic optic had created new scanning and imaging technologies to reveal images of human retina. The structural and functional information provide clinicians for more comprehensive eye diagnostic and treatment approaches. OCT is a non-invasive, non-contact imaging technique that visualizes the retina structure *in vivo* with high resolution. Huang *et al*. (2001) demonstrated the first cross sectional retinal imaging using OCT that made use of fibre optic Michelson low time-coherence (LTC) interferometry. The first *in vivo* tomogram of human optic disk and macula using OCT was shown by Fercher *et al*. (1993).

1.3.1 Principles of OCT

OCT is an imaging technique similar to ultrasound imaging except that it uses light instead of sound. In OCT, measuring the echo time delay and intensity of near-infrared light being backreflected and backscattered from different microstructure within a tissue, would produce cross sectional images at micrometer scale (Huang *et al*., 1991).

OCT uses light from a broadband light source which split into two at the beam splitter in an OCT system. One part of the input light is directed at the sample and the other sent to a reference mirror to obtain a reflectivity versus depth profile of the target tissue. The light waves were backscattered from tissue and interfered with the reference beam. Signals are routed back through the beam splitter and tracked by

photoreceptor in the OCT system. The returning pulses are used to measure light echoes versus the depth profile of target tissue *in vivo* (Huang *et al.,* 1991).

Presently, time-domain (TD) and spectral domain (SD) are two major technologies in producing OCT images. Although TD-OCT and SD-OCT were created concurrently, SD-OCT was only favoured after Wojtkowski *et al*. (2002) reported a better sensitivity in SD-OCT compared to TD-OCT. The authors reported theoretical and experimental results of better sensitivity of SD-OCT compared to TD- OCT. The researchers demonstrated SD-OCT sensitivity in excess of signal-to-noise ratio limit of TD-OCT.

TD technology was employed in the third generation Stratus OCT (Carl Zeiss Meditec, Inc, Dublin, CA). TD-OCT has scan rates of 400 A-scans per second with an axial resolution of 8–10 μm in tissue and a transverse resolution of approximately 20 μm. (Sull *et al*., 2010). SD-OCT superseded TD-OCT after its first commercial unit was introduced in 2006. By using an interferometer with a high-speed spectrometer, SD-OCT utilizes detection of light echoes simultaneously by measuring the interference spectrum. SD-OCT provides about twice the axial resolution of 5–7 μm in tissue with scan rates of 20 000–52 000 A-scans per second at 43-100 times scanning speed of TD-OCT (Wojtkowski *et al*., 2005).

1.3.2 Clinical use of OCT in paediatric ophthalmologic practices

OCT has the largest clinical impact on ophthalmology and used extensively for imaging macula and retinal nerve fiber layer (RNFL). OCT has been applied to study retinal retinal nerve fiber layer thickness (RNFLT) and macular thickness (MT) in amblyopic eyes. Early detection of amblyopia is crucial so that treatment can commence early to avoid loss of binocular function. Dickmann *et al.* (2009) studied the MT in children with strabismic amblyopia using Stratus OCT. They found meaningful difference in MT between strabismic amblyopic children and normal children. Using Cirrus OCT, Agrawal *et al.* (2014) reported mean MT was significantly thicker in strabismic amblyopic eyes [277.5 (15.3) μm] than in fellow eyes [272.4 (13.1) μm] (p=0.010). The observations might pave way for the utility of OCT in detecting amblyopia.

The application of OCT showed that children with juvenile glaucoma had thinner RNFL and macula when compared to their peers with normal vision. El-Dairi *et al.* (2009) measured the RNFLT and MT in 139 normal and glaucomatous eyes of children (age 4 -17 years) living in United States of America using Stratus OCT. They found that OCT measurements of RNFLT and MT were reduced with increasing grade of glaucomatous damage seen on stereophotographs. These OCT findings improve the diagnostic and monitoring of paediatric glaucoma paradigm.

Alisa-Victoria *et al*. (2014) reported the results of paediatric choroidal neovascularisation (CNV) secondary to Best's vitelliform macular dystrophy. The authors demonstrated the ability of OCT to visualize the subretinal reflection of subfoveal CNV with surrounding subretinal edema. Furthermore, the OCT images showed clear yolk-like lesion normally found in Best's disease. Progress was monitored by clinical eye examination, OCT and fundus fluorescein angiography. Kohly *et al*. (2011) observed that the effectiveness of anti-vascular endothelial growth factor (anti-VEGF) agents in treatment of paediatric CNV could be monitored using OCT.

OCT can be used to detect optic pathway gliomas (OPGs) in children with neurofibromatosis type 1 (NF1). OPGs are usually detected using expensive, laboriously magnetic resonance imaging (MRI). Chang *et al*. (2010) measured RNFLT in 9 children with NF1, 6 children with NF1 without OPGs and 15 controls using Stratus OCT. They reported NF1 children with OPGs had thinner RNFL (61 μm) when compared with age-match normal children (108 μm) ($p < 0.01$). NF1 children without OPGs have equivalent RNFLT as normal control children.

1.3.3 Reproducibility of OCT

Reproducibility of instruments' measurements is essential for detection, monitoring of progression and effectiveness of therapeutic management of the optic nerve disease. Good reproducibility of RNFL measurement has been reported with Cirrus SD-OCT in adults (Menke *et al*., 2008; Kim *et al*., 2009). Menke *et al*. (2008) measured the RNFLT in 38 normal eyes and reported mean ICC of 0.90. The mean coefficient of variation (COV) was 4.2% and 4% (range 1.9%–6.7%) for operator 1 and 2 respectively. Mean difference in RNFLT for ring 1 and 2 between the two operators were 0.9 μm and 0.1 μm respectively.

Reproducibility studies showed that OCT in children had the same level of reproducibility as in adults (Wang *et al.,* 2007; Eriksson *et al*., 2009; Altemir *et al*., 2013). Wang *et al.* (2007) reported reproducibility of RNFLT, MT and optic disk parameters using Stratus OCT. They included 2,353 year 7 students of 21 schools in Sydney. OCT measurements were performed by one operator and repeated between 2 sessions. Intraclass correlation coefficient (ICC) accounted for > 85%, > 62% and > 38% for MT, RNFLT and optic disk parameters respectively. Corresponding coefficients of variability were <5%, <8%, and <13%. The authors concluded that high reproducible measurements of MT and RNFLT could be obtained using Stratus OCT.

Eriksson *et al.* (2009) examined MT in 56 children aged 5-16 years using Stratus OCT and the system repeatability. The authors reported low intra-session COV of less than 2% in all areas of macula and high ICC of 0.9 However, they noted measurements of foveal minimum showed slightly higher COV of 4% and lower ICC of 0.693.

Altemir *et al*. (2013) used Cirrus OCT to obtain RNFLT and MT measurements in 100 Turkish children. They showed that all parameters assessed were highly reproducible. Intraobserver COV for RNFLT ranged from 2.24% to 5.52% and COV for MT was 0.97%. Intraobserver ICC was more than 0.8 for all parameters. Interobserver COV for RNFLT ranged from 2.23% to 5.18%.

Ghasia *et al*. (2012) examined 83 eyes of 83 American children with glaucoma, physiological cupping or normal. They aimed to compare the usage of SD-OCT with TD-OCT in children. They noted that SD-OCT was easier to obtain acceptable results than TD-OCT.

1.4 Retinal Nerve Fiber Layer Thickness

OCT studies showed that retinal thickness can be measured at micrometer level and reflect changes occurring. Comparison to age-matched population-based paediatric normative database is essential to detect deviations from the normal range. There are growing paediatric normative RNFLT databases studies to date. Huynh *et al.* (2006) of the Sydney Childhood Eye Study group reported RNFL measurements from Stratus OCT in 1543 six-year old children. Most of the children were European white (65.4%) and East Asian (15.9%). Ahn *et al.* (2005) reported RNFLT values in 72 children with mean age of 12.6 years. Salchow *et al.* (2006) measured RNFLT in 92 largely Hispanic children. El-Dairi *et al.* (2009) studied the RNFLT in 286 children predominantly black and white, aged 3-17 years. The mean average RNFLT of the normal children measured using TD-OCT ranges between 104.3 and 108.3 µm.

In Cirrus OCT study, Elia *et al.* (2012) reported the mean average RNFLT in Caucasian children aged 3-16 years as 98.5µm. Barrio-Barrio et al. (2013) reported RNFLT value in normal Caucasian children from 3 Spanish centres as 97.4µm. Al-Haddad *et al.*(2014) collected a normative database of RNFLT in 108 Middle Eastern healthy children aged 6-17 years using Cirrus OCT. They reported mean average RNFLT of 95.6 µm which was comparable to other Cirrus studies but lower than values recorded using RTVue-100 (109.4 µm) which is another type of SD-OCT (Tsai *et al.*, 2012).

The RNFL quadrant thickness showed a double hump pattern with the inferior being the thickest, followed by superior, nasal and temporal quadrant. The pattern was also known as Inferior, Superior, Nasal, Temporal (ISNT) rule. However, several reports showed exception to the rule (Ahn *et al.,* 2005; Huynh *et al.,* 2006; El-Dairi *et al.,* 2009).

1.5 Macular Thickness

Huynh *et al.* (2006), El-Dairi *et al.* (2009) and Eriksson *et al.* (2009) reported macular parameters in normal children using Stratus OCT. The mean average inner MT ranged between 264.3 and 279 µm while mean average outer MT ranged between 236.9 and 245.0 µm. The mean central MT was reported in a range between 188.8 and 204.0 µm.

Mean average MT in healthy children was thicker in SD-OCT compared to Stratus OCT. Mean average MT using Spectralis is the thickest (326.4 µm) (Turk *et al.*, 2012), followed by Cirrus; 279.6 µm (Al-Haddad *et al.*, 2014) and 283.6 µm (Barrio-Barrio *et al.*, 2013).

Al-Haddad *et al.* (2014) reported inner MT was statistically significantly thicker than outer macular in all quadrants. The findings were consistent with other reports using Stratus OCT (Eriksson *et al*., 2009; El-Dairi *et al*., 2009). The authors noted that discrepancies in reported normative databases could be due to ethnicity, race, gender, age, spherical equivalent and axial length measurements.

Huynh *et al.* (2006) observed that foveal minimum, central and inner macula was significantly thicker in white than in East Asian children, and in boys compared to girls. Similar gender differences association with central macula thickness was reported by Barrio-Barrio *et al.* (2013) and Al-Haddad *et al.* (2014), which was significantly thicker in boys than girls. All three research groups reported positive correlations between age and macular parameters.

1.6 Rationale of Study

As of today, there are still mixed results pertaining to the mean RNFLT and MT in strabismic eye and strabismic amblyopia eyes. We aimed to search for anatomical evidence in OCT measurements that would offer us better understanding on the possible involvement of the retina in the pathogenesis of strabismus and strabismic amblyopia.

The comparison of mean RNFLT and MT in previous studies (Altintas *et al*., 2005; Kee *et al*., 2006; Repka *et al*., 2006 Huynh *et al*., 2009; Alotaibi and Al Enazi, 2011; Dickmann *et al*., 2011; Park *et al*., 2011; Agrawal *et al*., 2013; Firat *et al*., 2013) was between strabismic amblyopia and normal eye. The results generally showed insignificant difference between the groups. However, there were lacking in literatures on the strabismic with good vision.

By including both strabismus with and without amblyopia into our strabismus group for comparison with normal eye of healthy subjects, we aimed to investigate the effects of abnormal binocular vision development towards possible changes in the retina. The comparison between strabismus with and without amblyopia might reveal new findings as both groups do not have binocular single vision.

The study participants consist of Malay ethnic children who are not exclusively found in Malaysia but also in our neighbouring countries. As of date, this is the first study in the South East Asian region that investigated on this topic. Furthermore, studies shown there are ethnic difference in mean RNFLT and MT. The sample size of normal children was not adequate for plotting the normative data but it could act as a reference for future studies.

2.1 General objective

To compare the retinal nerve fiber layer and macular thickness in Malay children with and without strabismus.

2.2 Specific objectives

1. To compare the mean retinal nerve fiber layer thickness in Malay children with and without strabismus.
2. To compare the mean macular thickness in Malay children with and without strabismus.
3. To compare the mean retinal nerve fiber layer thickness in strabismic Malay children with and without amblyopia.
4. To compare the mean macular thickness in strabismic Malay children with and without amblyopia.