Retinal Nerve Fiber Layer Thickness in Unilateral Amblyopia

May-Yung Yen, Ching-Yu Cheng, and An-Guor Wang

Purpose. To test the hypothesis that eyes with amblyopia may have thicker retina, retinal nerve fiber layer thickness (RNFLT) was investigated in patients with unilateral amblyopia.

Methods. Thirty-eight patients with unilateral amblyopia were studied. Among them, 20 patients had amblyopia with strabismus and 18 had refractive amblyopia without strabismus. Nineteen of 38 had anisometropia of 2.0 D or more. In addition, 17 patients with anisometropia of 2.0 D or more but without amblyopia were enrolled as control subjects. RNFLT was measured by optical coherence tomography with scan pattern "Nerve Head 2.0R" (Carl Zeiss Meditec, Dublin, CA). Average RNFLT was multiplied with their corresponding scan circumferences to estimate the integral values of the total RNFL area ($RNFLT_{estimated\ integrals}$).

Results. In all 38 patients with unilateral amblyopia, the difference in RNFLT and in $RNFLT_{estimated\ integrals}$ between the amblyopic eyes and the normal fellow eyes were statistically significant. Multivariate regression analysis with adjustment for axial length, spherical equivalence, age, and sex indicated significant differences as well. In the group of strabismic amblyopia, the difference in RNFLT and in $RNFLT_{estimated\ integrals}$ between the amblyopic eyes and the normal fellow eyes did not reach statistical significance. However, in the group of refractive amblyopia, the difference in RNFLT and in $RNFLT_{estimated\ integrals}$ between the amblyopia eyes and the normal fellow eyes both had a statistical significance. In the 19 patients with anisometropic amblyopia, the difference in RNFLT and in $RNFLT_{estimated\ integrals}$ between the amblyopic eyes and the normal fellow eyes were statistically significant. In the control group of 17 patients with nonamblyopic anisometropia, the difference in RNFLT and in $RNFLT_{estimated\ integrals}$ between both eyes did not reach statistical significance.

Conclusions. RNFLT may be affected by refractive amblyopia, but further histopathologic confirmation is needed. (*Invest Ophthalmol Vis Sci.* 2004;45:2224–2230) DOI:10.1167/iovs.03-0297

Amblyopia is considered to be a developmental disorder of spatial vision that is associated with the presence of strabismus, anisometropia, or form deprivation early in life.[1] If the same disorders occur later in life, amblyopia does not develop.

The amblyopic process may have an effect on various levels of the visual pathway. Shrinkage of cells in the lateral geniculate nucleus that receive input from the amblyopic eye[2–7] and a shift in the dominance pattern in the visual cortex[8–12] have been reported. Retinal involvement accompanying amblyopia is controversial.[13–17]

During fetal development, there is a rapid decline in cell density in the retinal ganglion cell layer toward the end of gestation. In humans, the total population of cells in the ganglion cell layer is highest (2.2–2.5 million cells) between approximately weeks 18 and 30 of gestation. After this, the cell population declines rapidly to 1.5 to 1.7 million cells.[18] The number of axons in the human optic nerve also decreases during gestation.[19] At 16 to 17 weeks of gestation, the estimated number of axons was 3.7 million. The number of axons in the human adult optic nerve is 1.1 million. In rat retina, the number of retinal ganglion cells projecting to the central visual nuclei is reduced by at least 35%, and the process ceases by 2 weeks postnatally.[20] If amblyopia affects the process of postnatal reduction of ganglion cells, RNFL thickness may be thicker than that in the normal eye. It was our plan to investigate retinal nerve fiber layer thickness (RNFLT) in amblyopic eyes to determine whether it is thicker.

Several techniques to evaluate the RNFLT, such as red-free ophthalmoscopy, scanning laser polarimetry (SLP) and optical coherence tomography (OCT) have been described. SLP estimates RNFLT based on the retardation of the laser beam caused by the birefringence of the RNFL. Because the cornea is also birefringent, erroneous RNFLT assessment can be made without proper anterior segment compensation.[21–23] OCT is a noninvasive, noncontact technique that measures RNFLT.[24,25] The RNFLT measured by OCT corresponds to the RNFLT measured histologically.[24] Because OCT is based on near-infrared interferometry, the thickness measurement is not affected by refractive status or axial length of the eye, nor by light changes in nuclear sclerotic cataract density.[26] RNFLT remains unchanged after laser-assisted in situ keratomileusis (LASIK).[27] Posterior subcapsular and cortical cataracts, heavy nuclear cataracts, secondary cataracts, loss of vitreous body transparency, and silicone oil in the vitreous chamber, however, reduce the ability to perform OCT.[26,28] Excluding these conditions, OCT is a reliable imaging technology. The purpose of our investigation was to use OCT to measure RNFLT in patients with unilateral amblyopia, to see whether the RNFL is thicker in the amblyopic eye.

Materials and Methods

Subjects

Approval for this project was obtained from the institutional review board of Taipei Veterans General Hospital. The study was performed according to the tenets of the Declaration of Helsinki for research involving human subjects. Patients with unilateral amblyopia were consecutively enrolled. Clinical examinations included best corrected visual acuity, refraction error, slit lamp examination, extraocular movements, intraocular pressure, fundoscopy, and A-scan for axial length. Patients with organic eye disease, a history or evidence of intraocular surgery, history of cataract, glaucoma, retinal disorders, or laser treat-

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TABLE 1. Basic Clinical Data of 20 Patients with Unilateral Amblyopia with Strabismus

Case	Gender	Age	Amblyopic Eye	Squint	BCVA	Refractive Error (D) A	Refractive Error (D) N	Axial Length (mm) A	Axial Length (mm) N	Average RNFLT (μm) A	Average RNFLT (μm) N
S1	M	12	OD	ET 25 PD	20/30	+0.75−5.5×180	−0.25−3.5×180	23.83	23.59	126	116
S2	M	22	OD	XT 40 PD	20/200	+4.0−7.0×180	−1.5×180	22.98	23.70	136	128
S3	F	50	OS	ET 40 PD	20/600	+7.0−3.5×60	+0.5	21.51	23.75	148	142
S4	F	13	OD	ET 40 PD	20/30	+2.75−2.75×180	Plano	22.26	23.07	147	133
S5	M	44	OS	XT 25 PD	20/30	+0.25−0.75×180	+1.5−1.5×180	23.90	23.25	137	124
S6	M	12	OD	XT 16 PD	20/1200	+0.5−3.5×180	−3.5−0.5×180	24.23	25.77	122	100
S7	F	58	OS	ET 16 PD	20/1200	+2.25−0.5×80	+1.75−1.0×125	22.85	22.70	128	121
S8	M	6	OD	ET 4 PD	20/200	+6.0	+4.0−1.0×180	19.85	20.04	114	120
S9	F	25	OS	XT 10 PD	20/50	+1.5	+0.5	21.27	21.42	146	185
S10	M	74	OS	ET, postop.	20/1200	+3.0−1.0×70	+3.25−1.0×50	23.63	23.41	121	133
S11	F	49	OS	ET 35 PD	20/1200	+2.25−1.0×150	+1.25−0.5×40	22.15	22.73	118	99
S12	M	15	OS	XT 35 PD	20/200	+1.0−1.25×180	−0.5	22.25	25.84	115	108
S13	M	20	OD	ET 10 PD	20/200	+0.25	−0.25	23.52	23.63	123	135
S14	F	23	OS	XT 90 PD	20/200	+3.25−1.5×180	−1.5−1.25×180	21.83	24.11	132	92
S15	F	20	OS	XT 30 PD	20/200	Plano	Plano	23.16	23.17	160	162
S16	M	10	OD	ET 40 PD	20/30	−0.25	Plano	24.08	23.01	126	128
S17	F	12	OD	XT 18 PD	20/100	−6.0−1.0×180	Plano	25.28	23.06	133	141
S18	M	20	OD	XT 12 PD	20/60	−6.0−7.5×180	3.0×180	26.07	24.20	122	123
S19	F	24	OS	XT 25 PD	20/200	−1.0−2.25×80	−9.5−1.0×10	23.81	28.06	128	129
S20	M	38	OD	XT 45 PD	20/60	−4.0−1.0×80	−3.0−1.0×120	26.26	25.02	147	146

A, amblyopia; N, normal; BCVA, best corrected visual acuity; ET, esotropia; XT, exotropia; PD, prism diopter.

ment and children not cooperative enough for OCT examination were excluded.

A total of 38 patients with unilateral amblyopia were enrolled. Twenty had strabismic amblyopia (Table 1). The other 18 without strabismus had a diagnosis of refractive amblyopia (Table 2). Of the 38 patients with unilateral amblyopia, 19 also had anisometropia, including 7 from the group with strabismic amblyopia and 12 from the group with refractive amblyopia (Table 3). Anisometropia was defined as a difference in spherical equivalence of 2.0 D or more between the two eyes. For the purpose of comparison, in addition, 17 patents with nonamblyopic anisometropia were enrolled as control subjects (Table 4).

OCT Technique

After obtaining informed consent, the pupils were dilated with 1 drop of 1% tropicamide. RNFLT was measured by OCT 30 minutes later. The OCT system used in this study was OCT model 2000 (Carl Zeiss Meditec, Dublin, CA). The software version was 5.1. A peripapillary circular scan with scan pattern "Nerve Head 2.0R" was carefully positioned. The same scan pattern was used in all cases. Internal fixation was chosen unless the amblyopia was too deep to follow the fixation target. Average RNFLT detected by the circular scan was measured three times in each eye. Figure 1 showed a single OCT scan. All OCT measurements were performed by one of the authors (C-YC) who was

TABLE 2. Basic Clinical Data of 18 Patients with Refractive Amblyopia without Strabismus

Case	Gender	Age	Amblyopic Eye	BCVA	Refractive Error (D) A	Refractive Error (D) N	Axial Length (mm) A	Axial Length (mm) N	Average RNFLT (μm) A	Average RNFLT (μm) N
R1	M	9	OD	20/40	+1.5−0.5×180	−0.75	20.05	23.99	150	130
R2	M	20	OS	20/100	+1.5−1.75×180	Plano	23.39	23.75	126	127
R3	M	9	OD	20/30	+4.0−0.5×160	Plano	22.14	23.06	154	130
R4	M	75	OD	20/60	+3.0−4.75×110	Plano	23.60	23.56	116	101
R5	M	18	OS	20/100	+3.75−0.75×180	+0.5−0.5×90	22.32	23.00	136	132
R6	M	71	OD	20/200	+4.75−1.5×90	+2.75−1.25×90	22.51	22.36	112	94
R7	M	23	OD	20/100	+0.5	−4.5−0.5×180	24.68	27.19	137	135
R8	F	22	OS	20/100	+4.0−0.5×180	−0.5−0.5×180	22.21	25.13	157	134
R9	M	28	OS	20/600	+5.0−1.5×35	−0.5×90	22.47	24.08	122	102
R10	F	20	OS	20/100	+2.0−1.0×180	−1.75−1.5×180	23.04	24.27	180	151
R11	F	21	OD	20/50	+1.5−0.75×90	−0.25	24.05	23.90	161	133
R12	F	8	OS	20/200	+2.5−0.75×180	+0.25−0.5×90	21.80	23.00	128	112
R13	F	33	OD	20/50	+5.25−1.5×160	+0.5−1.0×180	20.30	22.04	161	145
R14	M	25	OS	20/30	−2.0−2.0×180	−4.25−0.5×155	24.79	25.98	142	142
R15	M	10	OD	20/60	−4.25−1.0×40	−1.25	24.53	23.65	153	133
R16	M	24	OS	20/40	−5.25	−1.75	25.78	24.71	121	119
R17	M	20	OD	20/50	−0.25−4.0×50	−1.75−0.75×180	24.65	24.42	157	163
R18	F	21	OS	20/300	−6.0−2.5×60	Plano	25.60	23.18	147	152

A, amblyopia; N, normal; BCVA, best corrected visual acuity.

TABLE 3. Basic Clinical Data of 19 Patients with Amblyopia with Anisometropia

Case	Gender	Age	Amblyopic Eye	Squint	BCVA	Refractive Error (D)		Axial Length (mm)		Average RNFLT (μm)	
						A	N	A	N	A	N
S3	F	50	OS	ET 40 PD	20/600	+7.0−3.5×60	+0.5	21.51	23.75	148	142
S6	M	12	OD	XT 16 PD	20/1200	+0.5−3.5×180	−3.5−0.5×180	24.23	25.77	122	100
S8	M	6	OD	ET 4 PD	20/200	+6.0	+4.0−1.0×180	19.85	20.04	114	120
S14	F	23	OS	XT 90 PD	20/200	+3.25−1.5×180	−1.5−1.25×180	21.83	24.11	132	92
S17	F	12	OD	XT 18 PD	20/100	−6.0−1.0×180	Plano	25.28	23.06	133	141
S18	M	20	OD	XT 12 PD	20/60	−6.0−7.5×180	−3.0×180	26.07	24.20	122	123
S19	F	24	OS	XT 25 PD	20/200	−1.0−2.25×80	−9.5−1.0×10	23.81	28.06	128	129
R1	M	9	OD	ortho	20/40	+1.5−0.5×180	−0.75	20.05	23.99	150	130
R3	M	9	OD	ortho	20/30	+4.0−0.5×160	Plano	22.14	23.06	154	130
R5	M	18	OS	ortho	20/100	+3.75−0.75×180	+0.5−0.5×90	22.32	23.00	136	132
R7	M	23	OD	ortho	20/100	+0.5	−4.5−0.5×180	24.68	27.19	137	135
R8	F	22	OS	ortho	20/100	+4.0−0.5×180	−0.5−0.5×180	22.21	25.13	157	134
R9	M	28	OS	ortho	20/600	+5.0−1.5×35	−0.5×90	22.47	24.08	122	102
R10	F	20	OS	ortho	20/100	+2.0−1.0×180	−1.75−1.5×180	23.04	24.27	180	151
R12	F	8	OS	ortho	20/200	+2.5−0.75×180	+0.25−0.5×90	21.80	23.00	128	112
R13	F	33	OD	ortho	20/50	+5.25−1.5×160	+0.5−1.0×180	20.30	22.04	161	145
R15	M	10	OD	ortho	20/60	−4.25−1.0×40	−1.25	24.53	23.65	153	133
R16	M	24	OS	ortho	20/40	−5.25	−1.75	25.78	24.71	121	119
R18	F	21	OS	ortho	20/300	−6.0−2.5×60	Plano	25.60	23.18	147	152

A, amblyopia; N, normal; BCVA, best corrected visual acuity; ET, esotropia; XT, exotropia; PD, prism diopter; ortho, orthophoria.

not blind to the diagnosis. In every case, the right eye was always measured first, followed by the left eye.

Statistical Analysis

The mean of the three RNFLT measurement and $RNFLT_{estimated\ integrals}$[29] obtained from each eye were used for statistical analysis. Average RNFLT was multiplied with their corresponding scan circumferences to estimate the integral values of the total RNFL area: $RNFLT_{estimated\ integrals}$ (μm^2) = $RNFLT_{average}$ (μm) × scan circumference (μm). Results are presented as mean ± SD. A paired Student's *t*-test was used to assess the difference in RNFLT and in $RNFLT_{estimated\ integrals}$ between amblyopic and normal eyes in the patients with unilateral amblyopia and between both eyes of the patients with nonamblyopic anisometropia. $P < 0.05$ was considered to be statistically significant. To adjust for the possible effects of age, sex, refractive errors, and axial length on RNFL thickness, multivariate regression analysis was performed, and a generalized estimating equation[30] was used to account for the correlation between both eyes in individuals. The correlation between RNFL thickness and other continuous variables was determined using Spearman's rank correlation coefficient (ρ).

RESULTS

Among 38 patients with unilateral amblyopia, 23 were male and 15 were female. The mean ± SD age was 26.4 ± 18.3 years. The eye with amblyopia was the right eye in 19 patients and the left eye in 19 patients. Best corrected vision of the amblyopic eye ranged from 20/1200 to 20/30. Best corrected

TABLE 4. Basic Clinical Data of 17 Patients with Nonamblyopic Anisometropia

Case	Gender	Age	More Myopic Eye	Refractive Error (D)		Axial Length (mm)		Average RNFLT (μm)	
				More	Less	More	Less	More	Less
C1	F	26	OS	−8.75−0.5×135	−5.5−1.0×60	25.50	24.46	132	132
C2	F	22	OS	−7.75−1.5×180	−3.5−2.5×180	26.24	24.20	121	105
C3	M	53	OS	−5.5	−2.0−2.0×180	26.97	25.99	99	104
C4	F	22	OS	−5.25−0.75×50	+1.25−2.0×180	25.08	23.14	144	145
C5	M	35	OD	−5.25−0.5×180	−1.75−1.0×180	26.60	25.10	120	128
C6	F	14	OS	−5.0	−1.0	25.10	23.48	155	150
C7	F	20	OD	−5.0	−1.5	25.06	23.56	85	87
C8	F	27	OD	−4.75	−0.25−1.0×180	24.81	23.04	124	123
C9	F	14	OD	−4.5−2.0×180	−2.25−2.5×180	24.88	24.34	133	135
C10	M	26	OD	−4.5	−0.5	24.94	23.51	99	105
C11	M	41	OD	−4.25−0.5×90	−1.0−0.5×130	23.54	22.51	110	124
C12	F	14	OD	−3.5	+1.5−0.75×180	25.44	23.00	117	117
C13	F	43	OS	−3.0	−0.75	24.83	24.20	130	135
C14	M	12	OS	−2.0	Plano	23.31	22.76	154	142
C15	F	38	OD	−2.0	Plano	24.60	24.57	102	91
C16	M	35	OD	−1.75−0.75×180	Plano	24.00	23.86	141	141
C17	F	42	OS	−0.75−1.75×180	Plano	23.07	22.32	101	97

More, more myopic eye; Less, less myopic eye.

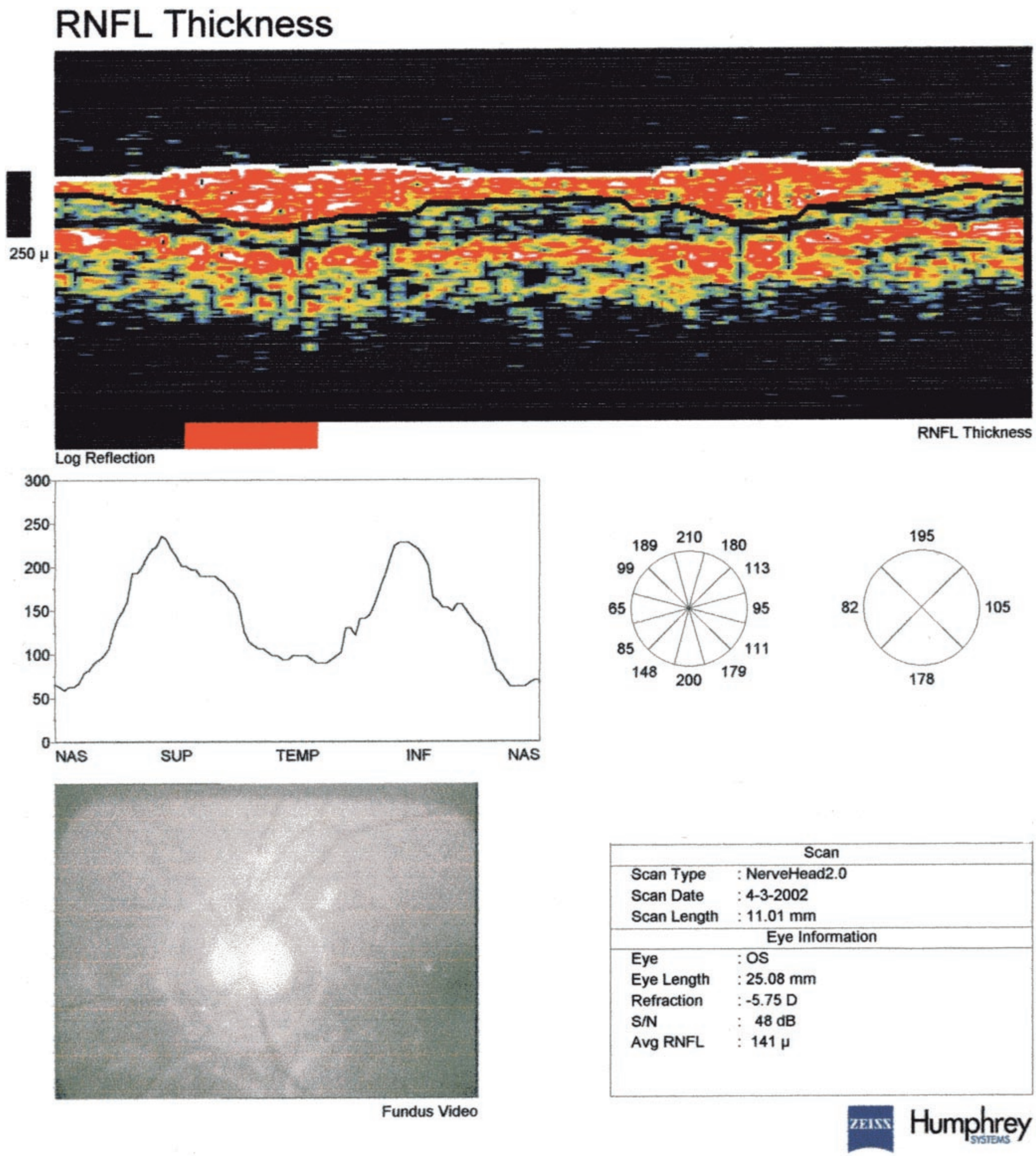

FIGURE 1. A single OCT scan of a normal eye.

vision of the normal eye was equal to or better than 20/20. The mean age of 20 patients with strabismic amblyopia was 27.4 ± 18.6 years, and the mean age of 18 patients with refractive amblyopia was 25.4 ± 18.6 years. The mean age of 17 normal control subjects was 28.5 ± 12.2 years.

In all 38 patients with unilateral amblyopia, the difference in RNFLT between the amblyopic eyes and the normal fellow eyes was statistically significant (Table 5). The difference in $\text{RNFLT}_{\text{estimated integrals}}$ between the amblyopic eyes and the normal fellow eyes was also statistically significant (Table 6). Multivariate regression analysis with adjustment for axial length, spherical equivalence, age, and sex indicated a significant difference in RNFLT and in $\text{RNFLT}_{\text{estimated integrals}}$ as well. Although the spherical equivalence in amblyopic eyes (0.17 ± 3.59 D) was higher than that in normal fellow eyes (−0.81 ± 2.33 D), the difference was not statistically significant (P = 0.084). In addition, there was no significant correlation between RNFLT and axial length ($\rho = -0.075$, $P = 0.655$) or

Table 5. Comparison of RNFL Thickness in Amblyopic and Normal Eyes

	Mean ± SD (μm)		Spherical Equivalence (D)		Axial Length (mm)		Paired-*t* Test (*P*)	Adjusted *P*
	Amblyopic	Normal	Amblyopic	Normal	Amblyopic	Normal		
Total patients ($n = 38$)	136.6 ± 16.5	128.9 ± 19.9	0.17 ± 3.59	−0.81 ± 2.33	23.40 ± 1.53	23.85 ± 1.46	0.003	0.006
Amblyopia with strabismus ($n = 20$)	131.5 ± 12.6	128.3 ± 21.5	−0.13 ± 3.6	−0.71 ± 2.82	23.39 ± 1.63	23.73 ± 1.66	0.085	0.500
Refractive amblyopia without strabismus ($n = 18$)	142.2 ± 18.6	129.7 ± 18.5	0.49 ± 3.57	−0.92 ± 1.70	23.41 ± 1.46	24.00 ± 1.23	<0.001	<0.001
Amblyopia with anisometropia ($n = 19$)	139.2 ± 17.2	127.5 ± 16.8	0.10 ± 4.73	−1.32 ± 1.83	23.18 ± 1.83	24.04 ± 1.75	0.001	<0.001

Adjusted *P*: multivariate regression analysis with generalized estimation equation, adjustment for spherical equivalence, axial length, age, and sex.

spherical equivalence ($\rho = -0.009$, $P = 0.956$) among all amblyopic eyes. RNFLT in all amblyopic eyes did not correlate with logMAR visual acuity ($P = 0.104$) after adjustment for age.

Further analysis was performed separately for strabismic and refractive amblyopia. In the group with strabismic amblyopia, the difference in RNFLT and $\text{RNFLT}_{\text{estimated integrals}}$ between the amblyopic eyes and the normal fellow eyes did not reach statistical significance. However, in the group of refractive amblyopia, the difference in RNFLT and in $\text{RNFLT}_{\text{estimated integrals}}$ between the amblyopic eyes and the normal fellow eyes were statistically significant (Tables 5, 6).

In the 19 patients with anisometropic amblyopia, the difference between RNFLT and $\text{RNFLT}_{\text{estimated integrals}}$ in the amblyopic eyes and in the normal fellow eyes both were statistically significant (Tables 5, 6). The differences were significant in the multivariate regression analysis as well. In the control group of 17 patients with nonamblyopic anisometropia, the difference in RNFLT and in $\text{RNFLT}_{\text{estimated integrals}}$ between the two eyes both did not reach statistical significance (Tables 7, 8).

Difference in RNFL thickness may come from glaucomatous damage and subjects older than 40 may confound the data analysis. Therefore, we also analyzed the data excluding subjects older than 40. The number of subjects was reduced to 31 from 38 (amblyopic) and to 13 from 17 (control). With a sample size of 31, the study had more than 80% statistical power to detect a 6% increase in RNFL thickness in amblyopic eyes, compared with the normal eyes. The results of RNFLT and $\text{RNFLT}_{\text{estimated integrals}}$ of the reduced number also consisted with the results of total number.

Discussion

During an OCT examination, the selected preset scan radius is automatically modified by the instrument's software. This modification is assumed to overcome the magnification produced by the patient's eye. The actual projected scan radius was found to have statistically significant positive correlation with axial length.[29] For each 1-mm increase in axial length, the actual projected scan radius increased approximately 0.06 mm or 3.5%. A final correction should be made by the examiner, by using a control knob, to reach the desired scan radius. This final correction of the actual projected scan radius, already modified by the instrument, should be made, especially in studies investigating the relationship of RNFL thickness measurement with axial length or refractive error. The study also found that the $\text{RNFLT}_{\text{estimated integrals}}$ area was found to be independent of the scan radius.[29] We did not correct the actual radius when we performed the OCT examination. Therefore, we used two approaches to correct for this. First, we used multivariate regression analysis to adjust the effects of refractive errors and axial length on the measured RNFLT. Second, we used the "retinal nerve fiber layer total area" as a proxy parameter. Our study revealed RNFLT was thicker and $\text{RNFLT}_{\text{estimated integrals}}$ were larger in the amblyopic eye, especially in refractive amblyopia and in anisometropic amblyopia, but not in strabismic amblyopia.

The amblyopic process may have an effect on various levels of the visual pathway. Histopathologic changes in the lateral geniculate nucleus and visual cortex have been reported.

Histologic study of the lateral geniculate nucleus of monkeys with strabismic, anisometropic, and visual deprivation amblyopia reveals marked shrinkage of cells that receive input from the amblyopic eye.[3–5] There are similar findings in the lateral geniculate nucleus in human anisometropic amblyopia[6] and strabismic amblyopia.[7]

Wiesel and Hubel[2,8,9] pioneered the application of microelectrode techniques to record directly from single neurons within the visual system of animals to study the effects of normal and abnormal visual experience early in life in visually immature kittens. Extracellular recordings from striate neurons in monkeys with strabismic, anisometropic, and visual deprivation amblyopia and in unilaterally lid-sutured kittens demonstrated a decimation of binocularly driven cells and of cells receiving input from the amblyopic eye.[10–12] In humans, positron emission tomography scans revealed a significant reduction of relative cortical blood flow and glucose metabolism

Table 6. Comparison of $\text{RNFLT}_{\text{estimated integrals}}$ in Amblyopic and Normal Eyes

	Amblyopic	Normal	Paired-*t* Test (*P*)	Adjusted *P*
Total patients ($n = 38$)	1,386,052 ± 199,609	1,326,627 ± 216,605	<0.001	0.006
Amblyopia with strabismus ($n = 20$)	1,359,696 ± 152,690	1,337,361 ± 215,409	0.507	0.500
Refractive amblyopia without strabismus ($n = 18$)	1,470,697 ± 207,649	1,376,891 ± 224,683	0.005	<0.001
Amblyopia with anisometropia ($n = 19$)	1,432,455 ± 188,711	1,342,034 ± 190,211	0.003	<0.001

Data are mean μm^2 ± SD. Adjusted *P*: multivariate regression analysis with generalized estimation equation, adjustment for spherical equivalence, axial length, age, and sex.

TABLE 7. Comparison of RNFL Thickness Between Eyes in Nonamblyopic Anisometropia

	Mean ± SD (μm)		Spherical Equivalence (D)		Axial Length (mm)		Paired-*t* Test (*P*)	Adjusted *P*
	More Myopia	Less Myopia	More Myopia	Less Myopia	More Myopia	Less Myopia		
Nonamblyopia with anisometropia (n = 17)	121.5 ± 20.4	121.2 ± 19.8	−4.51 ± 2.14	−1.41 ± 1.93	24.94 ± 1.07	23.76 ± 0.96	0.875	0.922

during visual stimulation of the amblyopic eye compared with the normal eye.[31]

Retinal involvement in strabismic and/or anisometropic amblyopia is controversial.[13–17] Electroretinograms elicited by patterned stimuli in humans with various types of amblyopia were significantly reduced.[13] The Stiles-Crawford effect or foveal visual pigment density, however, indicated no retinal dysfunction at the level of cone photoreceptors in amblyopic eyes.[14] There have been no studies of either the anatomic or physiologic properties of the retina in monkeys reared with experimental amblyopia due to strabismus or anisometropia. Ikeda and Tremain[15] reported that kittens reared with experimental esotropia had deficits in the spatial resolution of retinal ganglion cells in the area centralis of the deviating eye. Lid suture or surgical strabismus in cats, however, did not result in reduced ganglion cell resolution.[16,17] In the present study, the RNFL thickness measured by OCT was significantly thicker in refractive amblyopia.

Using a third generation nerve fiber analyzer (GDx; Laser Diagnostic Technologies, San Diego, CA), Colen et al.[32] measured RNFL thickness in strabismic amblyopia, and reported that there was no statistically significant difference between the strabismic amblyopic eyes and normal eyes. In the present study, RNFL thickness was not significantly different between strabismic amblyopic and normal eyes. However, the RNFL was thicker in refractive amblyopic eyes.

It is unclear why there is a difference in RNFL thickness between amblyopia associated with strabismus versus refractive error. Although strabismic and uncorrected refractive amblyopias are characterized by decreased visual acuity, psychophysical investigations[33–35] revealed substantial differences in the visual characteristics of humans with different types of amblyopia. Using a vernier grating stimulus, anisometropic amblyopes show hyperacuity, while strabismic amblyopes show severe losses in vernier acuity. In addition, strabismic amblyopes show "crowding effects" for vernier gratings, while anisometropic amblyopes show no such effects. The findings suggest that different neural losses are associated with amblyopias of different etiologies. In our study, the RNFL was thicker and $\text{RNFLT}_{\text{estimated integrals}}$ were larger in eyes with refractive amblyopia, suggesting that the process of postnatal reduction of ganglion cells require sharply focused objects as appropriate stimuli.

In conclusion, in refractive amblyopia, there is a thicker RNFL. This finding requires further histopathologic confirmation.

TABLE 8. Comparison of $\text{RNFLT}_{\text{estimated integrals}}$ between Eyes in Nonamblyopic Anisometropia

	More Myopia	Less Myopia	Paired-*t* Test (*P*)	Adjusted *P*
Nonamblyopia with anisometropia (n = 17)	1,327,434 ± 219,986	1,260,778 ± 204,979	0.009	0.847

Data are mean μm^2 ± SD.

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