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Original Article

Foveal Structural Analysis of Amblyopic Eyes with Two Types of Fixation Behavior by Spectral-Domain Optical Coherence Tomography

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We used spectral-domain optical coherence tomography (SD-OCT) to compare the foveal and parafoveal structures of 19 subjects aged 16-58 years (8 men, 11 women): 6 amblyopic patients with eccentric fixation, 5 amblyopic patients with central fixation, and 8 visually normal controls. We obtained foveal horizontal line scans using SD-OCT on all of the patients and controls. The total and layer thicknesses at foveal areas were analyzed. The mean (SD) ages of individuals in the eccentric fixation, central fixation, and control groups were 43.0 (13.9), 42.2 (16.3), and 38.5 (15.5) years, respectively. We observed no significant differences in the foveal or parafoveal retinal thicknesses at 500 and 1,500 μm from the foveal center among the 3 groups or between the amblyopic and fellow eyes. No significant differences were observed in the thickness of the ganglion cell complex layer or outer retinal layer at 500 and 1,500 μm from the foveal center among the three groups or between the two eyes. Overall, our SD-OCT analyses revealed no characteristic structural change in foveal regions in amblyopic eyes irrespective of the fixation behavior.

Key words: foveal structure, strabismic amblyopia, optical coherence tomography, eccentric fixation

Some individuals who have strabismic amblyopia cannot assume central fixation when the fellow eye is covered, and their amblyopic eye remains deviated; such patients who nonfoveolarly fixate are considered to have eccentric fixation. Steady and peripheral eccentric fixation is an unfavorable sign for treatment. Eccentric fixation is regarded as a relatively common event in patients with deep amblyopia [1]. Clinically, eccentric fixation occurs at an early age in which a marked interval elapses between the development of the strabismus and the initiation of treatment.

Functional assessments of various types of amblyopia have revealed that this condition results from an abnormal interaction between 2 eyes at higher levels of the central nervous visual system, but retinal structural changes have also been suspected as a cause. Histological studies using a deprivation model revealed various structural changes in the foveal region of animal retinas [2]. These concepts were supported by recent research using optical coherence tomography (OCT), which described changes in the foveal structure in the amblyopic eye; however, these findings remain debatable. Although some studies reported a significant increase in the macular and/or foveal thicknesses in amblyopic eyes [3-9], other studies did not [10-17]. Moreover, layer thickness analyses at parafoveal areas revealed thinning of the ganglion cell layer (GCL) and

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the inner plexiform layer (IPL) [12]. A reduction in the thickness of the outer nuclear layer (ONL) and an increase in the thickness of the inner nuclear layer (INL) were detected in amblyopic eyes [6]. We conducted the present study to compare foveal and parafoveal morphologies among amblyopic eyes with 2 types of fixation behavior, *i.e.*, central and eccentric fixation.

Subjects and Methods

Subjects. This age-matched cross-sectional study compared the foveal structure of amblyopic eyes with and without eccentric fixation. We enrolled 19 subjects aged 16-58 years (8 men, 11 women): 6 amblyopic patients with eccentric fixation, 5 unilateral amblyopic patients with central fixation, and 8 visually normal controls from among the patients who visited the Ophthalmology Outpatient Clinic of Ibara Municipal Hospital from June 2010 to February 2018. We obtained informed consent from each subject after explaining the nature and possible consequences of the study. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Ibara Municipal Hospital (Okayama, Japan).

Eligibility criteria. The inclusion criteria were: no medical history of any ocular disease (*e.g.*, cataract, glaucoma, or retinopathy), diabetes, systemic hypertension, or any other autoimmune or infectious disease. We used an ophthalmoscope equipped with a fixation target to detect and assess the fixation behavior. The fixation behavior was photographed with a fundus camera with a built-in fixation target (KOWA VX-10 Fundus Camera, Kowa Corp, Nagoya, Japan). For the visually normal controls, we assessed ocular dominance using the hole-in-card test to compare amblyopic eyes to non-dominant eyes, as well as to compare fellow eyes to dominant eyes.

We tested the visual acuity at a distance of 5 m with a decimal system, which was then converted to logMAR for statistical evaluations. We defined amblyopia as a corrected distant visual acuity of 0.155 logMAR (0.7 decimal) or worse, plus a minimum 3-line difference between the amblyopic and fellow eye. All of the subjects underwent an ophthalmic examination with an automated refractometer, slit-lamp biomicroscopy, and a fundus evaluation. We excluded all eyes with a refractive spherical equivalent (myopic or hyperopic) >6.0 diopter (D) or high astigmatism (>3D) from the study in order to decrease the effects of a refractive anomaly on OCT testing.

Spectral-domain optical coherence tomography. To obtain images of both eyes of all subjects following pupil dilatation, three-dimensional spectral-domain OCT (SD-OCT; 3D OCT-2000; Topcon Corp., Tokyo) was conducted by an experienced examiner (C.F.). The 3D OCT-2000 has an axial image resolution of 6 μm and imaging speed of 50,000 axial scans per second, and it includes a high-resolution 12.3-megapixel non-mydriatic color fundus camera. In each subject, the fovea was scanned in a horizontal direction for 6 mm using an A-scan with $1,024\times2$ pixels per line. To scan the center of the fovea of the amblyopic eyes with eccentric fixation, the patient was asked to fixate on an external fixation target using his or her fellow eyes, and the image was centered on the fovea by the examiner based on the fundus image generated by the SD-OCT system. Accurate scanning of the central fovea of amblyopic eyes with eccentric fixation was thus obtained, and the measurement errors were successfully decreased.

For better visualization during the analysis, all OCT images were converted to a grayscale. We used high-quality images with an image quality factor >70 for the image analysis. We also manually measured the total retinal thickness at five location points (the foveal center, and 500 and 1,500 μm nasally and temporally from the foveal center) and the individual retinal layer thicknesses as described later at 4 parafoveal points by using a caliper system provided with the OCT system. Two independent observers (F.K. and C.F.), who were blinded to whether an eye was amblyopic, measured the thicknesses twice and obtained averages; we used the mean of these values from the 2 observers as the thickness value for the analysis of each subject.

We measured the total retinal thickness from the inner aspect of the internal limiting membrane (ILM) to the outer aspect of the retinal pigment epithelium (RPE). The ganglion cell complex layer (GCC) comprised the retinal nerve fiber layer (RNFL), GCL, and IPL, and the outer retinal layer spanned from the inner surface of the outer plexiform layer (OPL) to the outer side of the outer segment (OS). We evaluated the foveal-to-parafoveal (1,000 μm from the foveal center) thickness ratio to assess the foveal pit depth [6]. Two independent observers (T.O. and F.K) quantitatively examined the presence of an ellipsoid zone (EZ) layer with a normal appearance [18] in the foveal region.

Statistical analysis. We used interobserver correlation coefficients (ICCs) for calculations to confirm the reproducibility of the measurements. Using the Kruskal-Wallis test followed by the Steel-Dwass test, we analyzed group differences among the 3 groups in the total and layer thicknesses and the foveal-to-parafoveal thickness ratio. The interocular differences between each subject's eyes were assessed using the Wilcoxon signed-rank test. Group differences in the rate of a normal-appearing EZ posterior to the fovea were determined with the chi-square test, and interocular differences were examined using McNemer's test. All statistical analyses were performed using commercial statistical software (JMP; SAS, Cary, NC, USA) and R (The R Foundation for Statistical Computing) with a graphical user interface, EZR (Saitama Medical Center, Jichi Medical University). We considered p-values < 0.05 significant.

Results

Significant differences were revealed in the best-corrected visual acuity (BCVA) of the amblyopic eyes ($p = 0.005$) and in the spherical equivalent values of the amblyopic eyes ($p = 0.016$) among the 3 groups tested. The BCVA values of the amblyopic eyes were worse in the eccentric and central fixation groups compared to those of the visually normal control subjects (1.02 logMAR, 0.10 decimal visual acuity for the eccentric fixation group; 0.55 logMAR, 0.28 decimal for the central fixation group; and −0.18 logMAR, 1.51 decimal for the visually normal control group). No significant difference in these parameters was noted between the two amblyopic groups. The amblyopic eyes with central fixation were significantly more hyperopic than both the amblyopic eyes with eccentric fixation and the controls; there was no significant difference between the eccentric fixation eyes and the visually normal eyes (Table 1).

All 6 of the patients with eccentric fixation had peripheral eccentricity; 4 of these patients showed nasal eccentricity and the other 2 had temporal eccentricity. Three of these patients had a paradoxical eccentric fixation with consecutive deviation following surgery.

The ICCs in the amblyopic eyes were highly reproducible. In the eccentric fixation group, the ICCs were 0.863-0.984 for the total retina, 0.802-0.931 for the GCC, and 0.842-0.974 for the outer retinal layer, whereas the ICCs of the amblyopic eyes in the central fixation group were 0.806-0.971 for the total retina, 0.831-0.958 for the GCC, and 0.839-0.961 for the outer retinal layer.

The total retinal thickness of the central fovea did not differ significantly among the 3 groups or between the 2 eyes of each subject in each group. The median (interquartile range) thicknesses of the central fovea in the amblyopic versus fellow eyes were as follows: eccentric fixation group, 214.0 (39.6) versus 216.6 (30.8) μm; central fixation group, 219.3 (33.1) versus 223.8 (38.6) μm; and control group, 212.0 (14.8) versus 211.6 (15.4) μm. The total retinal thicknesses at the four parafoveal points (at 500 and 1,500 μm nasally and temporally) did not significantly differ between the amblyopic and fellow eyes in the eccentric and central fixation groups or between the patients with amblyopia and the visually normal control group (Fig. 1).

We observed no significant differences in the thickness of the GCC or the outer retinal layer among the three groups or between the 2 eyes of each subject in each group (Fig. 2 and 3). The ratio of the thickness of the central fovea to the parafovea at 1,000 μm nasally and temporally did not differ significantly among the 3 groups or between the 2 eyes (Fig. 4). In addition, we observed no significant group or interocular differences in the rate of a bulge-shaped foveal EZ. A bulge-shaped EZ was detected in 100% of the amblyopic eyes in the eccentric and central fixation groups (Table 2).

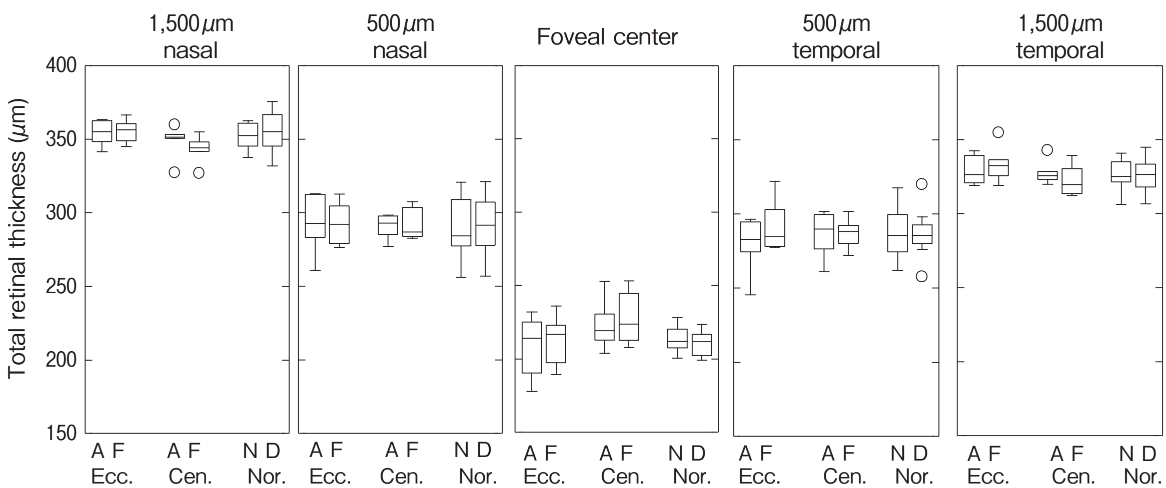
Discussion

Our analyses revealed no significant morphological differences in the foveal regions of amblyopic eyes irrespective of their fixation behavior. Regarding the total thicknesses of the central fovea and the four parafoveal points, no significant differences were noted between the amblyopic and fellow eyes in the eccentric and central fixation groups or among the eccentric fixation, central fixation, and visually normal control groups. Some studies have reported thicker fovea in amblyopic eyes than in fellow eyes [3-6, 8-10] or control eyes [3, 7]. Corroborating our findings, some studies have reported no significant differences between amblyopic and fellow eyes [11-17], amblyopia and normal control groups [13-15, 17], and anisometropic and strabismic

Table 1 Characteristics of the subjects in the two amblyopia groups and control group

	Amblyopia with eccentric fixation n=6	Amblyopia with central fixation n=5	Visually normal control n=8	*p* value[a]
Age (years)				
Mean (SD)	43.0 (13.9)	42.2 (16.3)	38.5 (15.5)	0.959
Range	17 to 54	16 to 58	18 to 58	
Gender, No. (%)				
Male	4 (66.7)	1 (20.0)	3 (37.5)	0.279
Female	2 (33.3)	4 (80.0)	5 (62.5)	
Type of amblyopia, No. (%)				
Strabismus	4 (66.7)	1 (20.0)	NA	0.047
Anisometropia	0 (0)	3 (60.0)		
Combination	2 (33.3)	1 (20.0)		
BCVA				
Amblyopic eye				
(logMAR) Mean (SD)	1.02 (0.32)	0.55 (0.16)	0.18 (0.06)	0.005
Range	0.40 to 1.30	0.30 to 0.70	−0.30 to −0.08	
(Decimal) Mean	0.1	0.28	1.51	
Fellow eye				
(logMAR) Mean (SD)	−0.21 (0.06)	−0.18 (0)	−0.14 (0.08)	0.099
Range	−0.30 to −0.18	−0.18 to −0.18	−0.30 to −0.08	
(Decimal) Mean	1.62	1. 5	1.40	
Mean spherical error (D)				
Amblyopic eye				
Mean (SD)	−1.08 (2.35)	+3.45 (2.39)	−1.92 (2.05)	0.016
Range	−5.63 to +0.63	−0.13 to +6.00	−4.50 to +0.63	
Fellow eye				
Mean (SD)	−2.35 (2.93)	−1.30 (1.11)	−1.56 (1.78)	0.904
Range	−7.38 to 0	−3.13 to −0.13	−3.88 to +0.63	

BCVA best corrected visual acuity, D diopters sphere.
[a]Chi-squared test or Wilcoxon rank sum test.



A, amblyopic eye; F, fellow eye; D, dominant eye; N, non-dominant eye;
Ecc, amblyopia with eccentric fixation; Cen, amblyopia with central fixation; Nor, visually normal control.

Fig. 1 The total retinal thicknesses at five foveal areas—*i.e.*, the foveal center, and 500 μm and 1,500 μm nasal and temporal to the foveal center—in amblyopic versus fellow eyes in 3 groups.

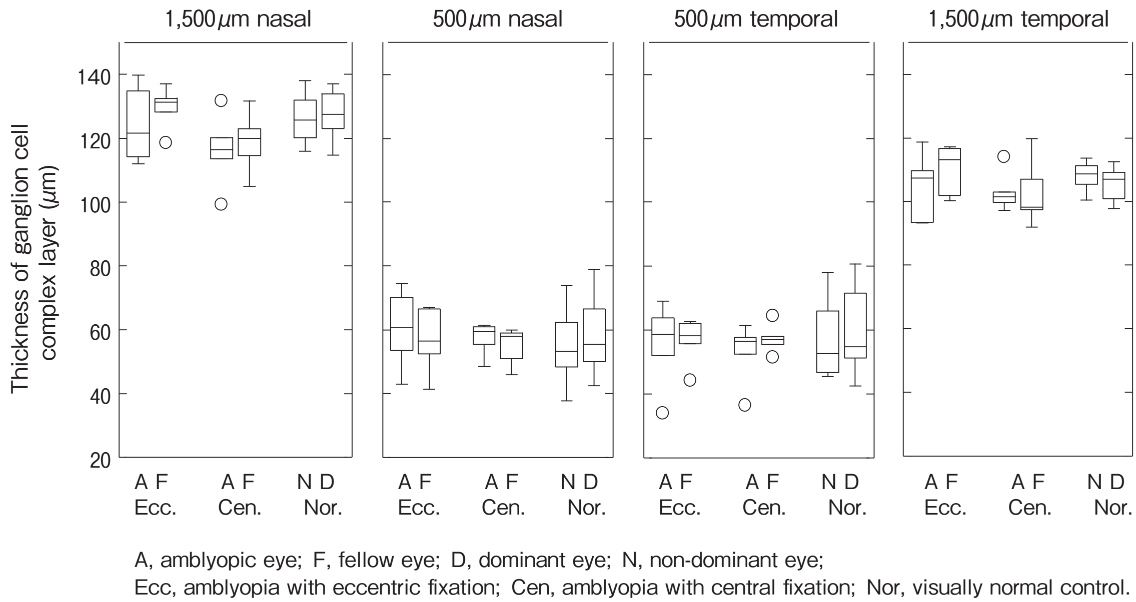


Fig. 2 Ganglion cell complex (GCC) layer thicknesses at foveal areas in amblyopic versus fellow eyes in 3 groups. GCC layer: From the retinal nerve fiber layer (RNFL) to the inner plexiform layer (IPL).

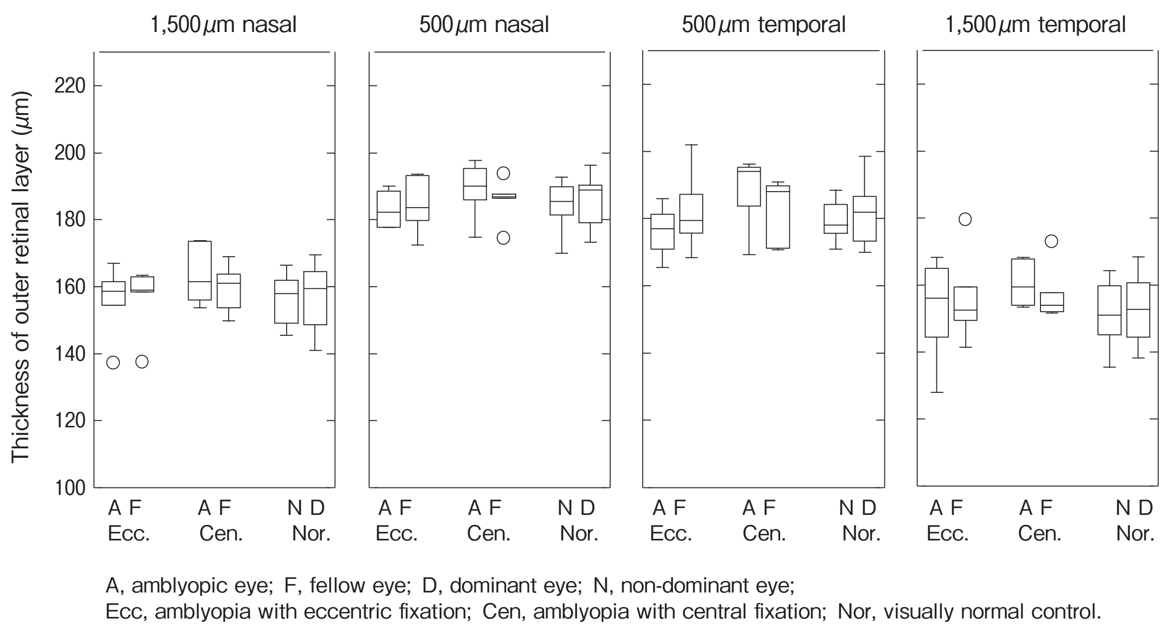
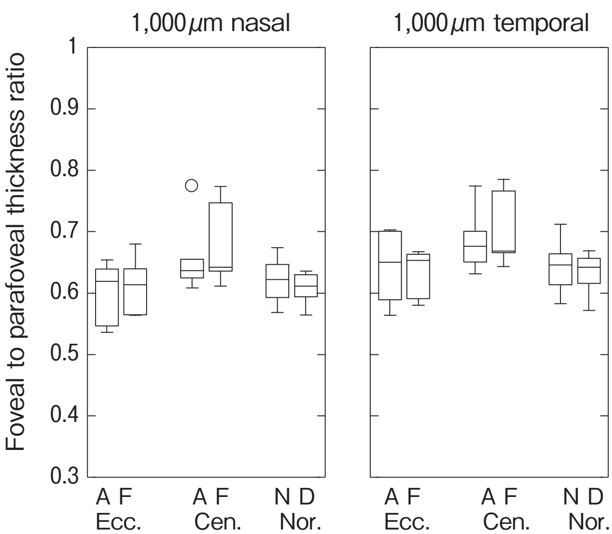


Fig. 3 Outer retinal layer thicknesses at foveal areas in amblyopic versus fellow eyes in three groups. Outer retinal layer: From the inner surface of the outer plexiform layer (OPL) to the outer side of the outer segment (OS).

amblyopia [6,16]. Walker *et al.* [11] reported no significant difference in retinal thicknesses in 8 quadrant Early Treatment Diabetic Retinopathy Study (ETDRS) sectors between amblyopic and fellow eyes, which is consistent with our results. Conversely, other studies reported that significant differences in the retinal thickness in anisometropic amblyopic eyes depended on the foveal region [3,9,13,14].

The inconsistent findings mentioned above could be partly attributable to the different types of OCT instruments and measurement protocols used, and to differences in the subjects (*e.g.*, strabismic vs. anisometropic amblyopia). In several recent studies, the mean macular thickness was measured automatically by SD-OCT or swept-source (SS)-OCT with divisions into 9 quadrant sectors using an ETDRS grid comprising 3 concentric circles with diameters of 1, 3, and 6 mm, and no notable differences in the foveal thickness of amblyopic eyes were reported [5, 11-17]. It is thus worth noting that the studies which did report a significant difference in the foveal thickness of amblyopic eyes were generally performed using time domain (TD)-OCT [3, 4, 7, 8] or manual measurements with calipers [6, 7]. TD-OCT has a lower scan speed and a larger image-resolution limit than SD- and SS-OCT; the lower quality of the images and less accurate scanning of the center of the fovea in amblyopic eyes with unstable fixation may thus have contributed to the thicker fovea in amblyopic eyes than in fellow eyes. Manual measurement using calipers, which requires using a broader area than only the precise central point, could also account for the incorrect assessment of foveal or parafoveal thicknesses.



A, amblyopic eye; F, fellow eye; D, dominant eye;
N, non-dominant eye;
Ecc, amblyopia with eccentric fixation; Cen, amblyopia with central fixation; Nor, visually normal control.

Fig. 4 The foveal-to-parafoveal thickness ratio at 1,000 μm from the foveal center in the 3 subject groups.

Differences in the type of amblyopia could contribute to the variations in the central foveal and/or parafoveal retinal thickness. Differences in foveal or parafoveal thicknesses were reported between strabismic and anisometropic amblyopia. In some studies, the foveal area in amblyopic eyes was thicker than that in fellow eyes in patients with strabismic amblyopia, but not in those with anisometropic amblyopia [8, 10]. Conversely, other investigations reported thicker central macula [5] or some parafoveal retinal regions [14] in amblyopic eyes compared to the fellow eyes in anisometropic amblyopia, but not in strabismic amblyopia. Nevertheless, we did not observe any significant differences in the total retinal thicknesses between the amblyopic and fellow eyes at the central fovea and the four parafoveal points in the present eccentric fixation group.

Regarding the layer thicknesses, various changes in amblyopic eyes have been reported. For example, an increased INL accompanying a reduced ONL was reported in amblyopic eyes [6], suggesting foveal immaturity based on the findings of a histological study [19]. In anisometropic amblyopia, the GCC [10] and RNFL are thicker in amblyopic eyes and the myoid zone and ellipsoid zone are thicker in fellow eyes than those

Table 2 A bulge-shaped foveal ellipsoid zone (EZ) in amblyopia and normal control groups

	Eyes	Amblyopia with eccentric fixation n = 6	Amblyopia with central fixation n = 5	Visually normal control n = 8	p value[a]
Presence of EZ,	Amblyopic	6 (100)	5 (100)	6 (75.0)	0.215
No. (%)	Fellow	6 (100)	4 (80.0)	7 (87.5)	0.544
	p value[b] (Amblyopic vs. Fellow)			0.48	

EZ bulge-shaped foveal ellipsoid zone, [a]Chi-squared test, [b]McNemar's test.

in normal eyes [7], indicating that the fellow eyes of amblyopic patients change during the amblyopic development. Another study reported a thinner GCL + IPL at parafoveal areas in amblyopic eyes, suggesting that retrograde degeneration originated in the striate cortex [12]. In the present study, we observed neither interocular nor group differences in the GCC or outer retinal layer thicknesses. Likewise, Araki *et al*. [14] reported no significant differences in the macular RNFL, GCL + IPL, or GCC thicknesses among amblyopic, fellow, and control eyes.

A shallow foveal pit could be one of the signs of foveal immaturity [20]. The ratio of the thickness of the central fovea to that of the parafovea at 500 and 1,000 μm was measured as the shallowness of the foveal pit, and a significantly higher ratio was observed in the amblyopic eyes compared to the fellow eyes [6]. Vajzovic *et al*. [21] demonstrated that the height of the foveal EZ layer was increased, which they described as "bulge-shaped," during development because of cone packing. Al-Haddad *et al*. [6] reported an attenuated or absent bulge in the EZ layer in 60% and 29% of amblyopic and fellow eyes, respectively. They thus considered the bulge-shaped EZ layer a sign for a normal foveal architecture, suggesting that an attenuated or absent bulge at the EZ layer represented underdeveloped photoreceptors. Contrarily, we found neither interocular nor group differences in the foveal pit depth, and we detected a bulge-shaped EZ layer in all amblyopic eyes in both the eccentric and central fixation groups.

This study has some limitations. The primary limitation was the small sample size (19 patients). Another limitation was the presence of magnification errors based on individual axial lengths, spherical refraction, cylinder refraction, and the corneal radius, which needed correction. We performed parameter adjustments for sex and age, but since our patients were aged 17-58 years, our findings might have been affected by aging. A third limitation is the differences in measurement accuracies between the eccentric fixation group and the other two groups because of the non-central and unstable fixation, worsening the accuracy of the scanning and the quality of the images. Nevertheless, the bulge-shaped EZ was detected in all amblyopic eyes, and the high ICCs revealed in all 3 groups are indicative of accurate measurements.

In conclusion, our study revealed no characteristic structural changes in foveal regions irrespective of the eyes' fixation behavior. These findings suggest that amblyopia with eccentric fixation is not a result of morphological change in the foveal region.

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