Retinal Thickness and P-ERG Changes in Adult Patients With Anisometropic and Strabismic Amblyopia

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Research Article

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Abstract

Objective

To investigate the changes of retinal thickness and P-ERG signals in adult patients with anisometropic and strabismic amblyopia.

Methods

Sixty patients with monocular adult amblyopia, including 30 anisometropic amblyopes (AA group) and 30 strabismic amblyopes (SA group), were enrolled in our study at the outpatient clinic of The Hefei First People's Hospital Hospital of Anhui medical University from June 2019 to November 2020. Retinal nerve fiber layer (RNFL) thickness was measured within 3.4 mm diameter range surrounding the optic nerve, and ganglion cell complex (GCC) layer thickness within 6 mm diameter range surrounding the fovea by an Optovue RTVue OCT in both amblyopic and fellow eyes. The amplitude and latency of P_{50} and N_{95} in P-ERG were recorded by a Roland electrophysiology instrument under two stimulation conditions with different temporal and spatial frequencies that were designed to bias the parvocellular and magnocellular pathways respectively. Data between amblyopic and fellow eyes was statistically analyzed by paired t test. The correlation between axial length and parameters of OCT and P-ERG was examined by Pearson correlation test.

Results

(1) Changes in RNFL thickness: In the AA group, RNFL thickness in temporal sector was significantly thinner ($p = 0.033$), while that in the nasal, superior and inferior sectors increased ($p < 0.05$) compared with fellow eyes. In SA group, no significant difference (each sector $p > 0.05$) was found between amblyopic eyes and fellow eyes. (2) Changes in GCC thickness: Compared with fellow eyes, in the AA group, GCC layer thickness of amblyopic eyes was significantly increased ($p = 0.039$), whereas in the SA group, we did not find a significant difference between amblyopic eyes and fellow eyes ($p > 0.05$). (3) P-ERG stimulated mode biased the parvocellular pathway: When compared with fellow eyes ($n = 15$), in the AA group, the amplitudes of P_{50} ($p = 0.004$) and N_{95} ($p = 0.038$) were significantly decreased in amblyopic eyes, but no significant latent time difference ($p > 0.05$) was found. In the same stimulus pattern, no statistically significant difference ($n = 15$, $p > 0.05$) between amblyopic eyes and fellow eyes was found in the amplitude and latency of P_{50} and N_{95} in the SA group. (4) P-ERG stimulated mode biased the magnocellular pathway: The amplitude and latency of P_{50} and N_{95} showed no statistically significant difference ($p > 0.05$) in either the AA group or the SA group. (5) We found no significant correlation between axial length and OCT, P-ERG parameters ($p > 0.05$) in either group.

Conclusion

Our results showed that the alterations in structure and function of retina that could be seen in adult anisometropic amblyopia were not found in adult strabismic amblyopia group. The functional loss in anisometropic amblyopia was found to bias to a damage of partial ganglion cells by the parvocellular pathway. These findings indicated that the pathological mechanisms were different between anisometropic and strabismic amblyopia.

Introduction

Abnormal visual input in critical period, commonly due to anisometropia or strabismus, results in amblyopia (mostly unilateral), whose visual acuity can't be corrected to normal, with an incidence rate of 1–5% [1]. Causes for amblyopia include strabismus, anisometropia, form deprivation, and uncorrected refractive errors during the sensitive period of visual system development, but the pathophysiological mechanism of amblyopia is still unclear [2]. Von Noordent et al. [3] and Wiesel TN et al. [4], through animal experiments, found that amblyopia could affect the development of lateral geniculate body cells, leading to abnormal cell morphology. These geniculate body neurons are responsible for receiving the eyes' visual signals and project signals onto the visual cortex. Previous pattern reversal visual evoked potentials (PVEP) studies also showed that the amplitude and latency time of P_{100} wave were significantly decreased in amblyopic eyes [5, 6]. These studies revealed that in amblyopia, structural and functional alterations could be seen in the visual cortex and subcortical area.

Are there any structural and functional changes that can be found in the retina in patients with amblyopia? In recent years, the wide application of the spectral domain OCT (SD-OCT) has made it possible to measure the thickness of the retinal nerve fiber layer. Altintas et al. [7], Al-Haddad et al. [8], with the use of an OCT, found no significant difference in retinal nerve fiber layer (RNFL) thickness in patients with anisometropic amblyopia when comparing their amblyopic eyes with the fellow eyes. However, Yoon et al. [9] also used OCT to examine children ages 5 to 12 with anisometropic amblyopia and found that these patients' RNFL thickness increased in the amblyopic eyes when compared to the fellow healthy eyes. The above-mentioned research reflects contradictory results of RNFL thickness changes in amblyopic eyes. The present consensus regarding structural changes in the retina of patients with amblyopia mainly focuses on the ganglion cells alternations after birth [10, 11]. The ganglion cell complex (GCC), comprising the nerve fiber layer, ganglion cell layer, and inner plexiform layer, is a good indicator of ganglion cells status. Park et al. [12] and Tugcu et al. [13] measured amblyopic patients' GCC thickness but arrived at opposite results. Park et al. found GCC thickness in amblyopic eyes reduced when compared to fellow healthy eyes. Tugcu et al., on the other hand, found that patients with anisometropic amblyopia had a significant increase in GCC thickness in the amblyopic eyes.

Pattern-electroretinogram (P-ERG) reflects the function of retina, especially the ganglion cells function. Arden et al. [14] found that P_{50} amplitude of amblyopia eyes in 6 to 28 year old patients with anisometropic and ametropic amblyopia is smaller than that of normal control eyes; but other researchers such as Guttob et al. [15] and Hess et al. [16] reported that the amblyopic eyes, comparing to normal control group, showed no significant difference in P-ERG in any type of amblyopia.

Whether or not structural or functional changes of the retinal are present in amblyopia has been of interest to many researchers, but results have been conflicting. Three reasons may be behind this, including: (1) Age factor: Some studies were based on children's visual sensitive period for the study. Children's visual development and plasticity are different from those of an adult, and so direct comparison may produce conflicting conclusions; (2) Different types of amblyopia become a confounding factor; and (3) Racial differences and potential measurement errors are also considered as potential confounding factors [17].

With the goal to explore retinal changes of adult amblyopia, we used OCT and PERG to investigate the functional and structural alternations of retinal in anisometropic and strabismic amblyopes.

Subjects And Methods

Participants

30 cases of adult anisometropic amblyopia (AA) and 30 cases of adult strabismic amblyopia (SA), age 21.35 ± 2.14 years (Mean ± SD), were recruited at the eye outpatient clinic of the Hefei First People's Hospital of Anhui medical University from June 2019 to November 2020. All subjects were of Chinese origin with a male to female ratio close to 1:1. The visual acuity of the amblyopic eyes in the AA group was 0.509 ± 0.333 logMAR, and in the SA group, 0.611 ± 0.277 logMAR. The study was approved by the ethics committee of the Hefei First People's Hospital of Anhui medical University University and followed the Declaration of Helsinki. Written informed consent was obtained from all subjects.

The subjects' best corrected visual acuity (BCVA) in the amblyopic eye was required to be ≥ 0.222 logMAR, and the fellow healthy eye's BCVA was required to be ≤ 0 logMAR. Subjects were excluded if there was any anterior segment, fundus disease, or previous ocular surgery, or if there was any systemic disease that may affect the eyes. Both amblyopic and fellow eye in each subject were required to have normal central fixation.

In the AA group, only subjects with a refractive error difference of spherical power greater than 3.0D between the two eyes, and cylindrical power difference of greater than 1.0D, were included. In the SA group, subjects with an interocular difference of spherical power ≤ 1.5D, and cylindrical power difference of < 1.0D, were included. Characteristics of AA and SA patients are shown in Table 1. Data were presented as mean ± SD.

Table 1
Characteristics of Two amblyopic groups

	AE		FE	
	AA	SA	AA	SA
Age	21.32 ± 2.81		22.43 ± 1.47	
Gender (percent female)	52.63%		47.14%	
Race (percent Asians)	100%		100%	
BCVA (log MAR)	0.509 ± 0.330	0.511 ± 0.277	-0.039 ± 0.094	-0.001 ± 0.027
spherical equivalent	1.75 ± 0.56	-2.00 ± 0.48	-2.13 ± 1.03	-1.79 ± 0.80
AL(mm)	24.2 ± 0.586	24.7 ± 0.443	25.1 ± 0.514	25.4 ± 0.112

AE: amblyopic eye; FE: fellow eye; AA: anisometropic amblyopia group; SA: strabismic amblyopia group; BCVA: best corrected visual acuity; AL: axial length.

Data were presented as Mean ± SD.
The tabular dates are presented as Mean ± SD. No significant correlation was found between axial length and the results from the OCT or P-ERG (Pearson's Correlation, $p > 0.05$).

Abbreviation: AA, anisometropic amblyopia; SA□strabismic amblyopia; BCVA□best corrected visual acuity□AL□axial length.

Examination methods

1. General Examination:

The anterior segment was examined by a slip-lamp, and the fundus was checked with a direct ophthalmoscopy. BCVA was measured with the Snellen chart at a distance of 5 m and converted into logMAR values for statistical analysis. Intraocular pressure was measured by applanation tonometry prior to instillation of tropicamide eye drops, three times in total. Axial length (AL) was measured with a Lenstar LS 900 (LS 900® Haag-Streit AG, Koeniz, Switzerland). Cover test with prism was applied to identify the presence of strabismus and the degree of strabismus.

2. OCT Examination:

Optovue RTVue (RTVue-100, version 2.0.4.0, Optovue Inc., Fremont, Canada) Fourier-domain OCT imaging technology was used in this study. OCT examination was completed with a natural pupil size, and by the same skilled examiner. RNFL thickness within a 3.4mm diameter range surrounding the optic nerve (ONH scan) and GCC thickness within 6mm diameter range using the fovea as the center (GCC scan) were

measured in all amblyopic and fellow healthy eyes. The RNFL thickness of four sectors (T: temporal, S: superior, N: nasal, I: inferior) [18] was analyzed (Fig. 1a).

3. P-ERG Examination

The Roland electrophysiology instrument (ROLAND CONSULT, Color Ganzfeld 0450C, Germany) was utilized to record P-ERG. Subjects wore glasses to maintain BCVA and were asked to sit in a dim room (average luminance of 5 cd/m^2). Before the test, each subject was given 10 minutes for dark adaptation and a pupil diameter of about 5 mm was maintained with no mydriatic or miotic. Display contrast was 80%, and the average brightness was 110 cd/m^2. Subjects were positioned 1 m away from the monitor. The following two different P-ERG stimulation patterns were used: the magnocellular pathway biased stimulation modes: low spatial frequency (4c/d) - high temporal frequency (8 Hz) (LS-HT model); and the parvocellular pathway biased stimulation modes: high spatial frequency (12c/d) - low temporal frequency (1 Hz) (HS-LT model) [19]. Silver chloride skin electrodes were placed on both sides of the lower eyelid and temples as a recording line and forehead acted as a ground reference line. Each stimulus flipped 200 times in a row to be superimposed and recording electrical impedance remained below 5Ω. The recording signal was amplified 50,000 times by the dual differential amplifiers. Filters were set between 1Hz and 30Hz. The computer automatically recorded the steady-state P-ERGs near sinusoidal by Fourier transformation. P_{50}, N_{95} amplitude and latency were analyzed.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc, Chicago, IL). Significant level of P values is ≤ 0.05. OCT and P-ERG parameters were compared by using paired t test. The correlation between the axial length (AL) and parameters of OCT, P-ERG was analyzed by using the Pearson correlation test.

Results

(1) Changes of RNFL thickness in anisometropic amblyopia and strabismic amblyopia patients:

RNFL thickness of amblyopic eyes was significantly thinner in the AA group in the temporal sector than that of the fellow healthy eyes ($n = 15$, $p < 0.05$), but in the other three sectors (nasal, superior, and inferior), RNFL thickness significantly increased compared with the fellow eyes ($n = 15$, $p < 0.05$) by an OCT examination (Fig. 1b). In the SA group eyes, no statistically significant difference was found in RNFL thickness of the four sectors compared with the fellow healthy eyes ($p > 0.05$).

(2) Changes of GCC thickness in anisometropic amblyopia and strabismic amblyopia patients:

GCC layer thickness in the amblyopic eyes significantly increased compared with the fellow healthy eyes in the AA group ($n = 15$, $p < 0.05$). But in the SA group, there was no statistically significant difference compared to the fellow eyes ($p > 0.05$) (Fig. 2).

(3) P-ERG findings in anisometropic amblyopia and strabismic amblyopia patients.

P-ERG in parvocellular pathway biased stimulated mode: Compared with the fellow healthy eyes, P_{50} amplitude ($n = 15$, $t = -3.329$, $p < 0.05$) and N_{95} amplitude ($n = 15$, $t = -2.235$, $p < 0.05$) significantly decreased, but there was no significant difference ($p > 0.05$) in latency in the AA group. While there was no significant difference in P_{50}, N_{95} amplitude and latency in the SA group ($p > 0.05$). P-ERG in magnocellular pathway biased stimulated mode: No significant difference was found in amplitude and latency in both the AA and SA groups ($p > 0.05$) (Table 2).

Table 2
The latency and amplitude of P-ERG in amblyopia patients

		Mean		t	
		AE	**FE**	**t**	**p**
HS-LT-model	P_{50} Latency	1.700	1.920	-0.797	0.436
	N_{95} Latency	4.883	3.558	-1.578	0.133
	P_{50} Amplitude	0.366	0.533	-4.108	0.001
	N_{95} Amplitude	0.573	0.806	-3.126	0.006
LS-HT-model	P_{50} Latency	1.872	7.250	1.903	0.074
	N_{95} Latency	0.183	2.583	0.097	0.924
	P_{50} Amplitude	0.002	0.159	0.010	0.992
	N_{95} Amplitude	0.025	1.118	0.084	0.934

The table shows the latency and amplitude of P-ERG waves produced by the LS-HT and HS-LT stimulation in the AA group; the italic bold text shows the decrease of the amplitude of AA patients' P50 and N95 in the stimulations. The amplitude decrease of amblyopic eyes of AA patients is significantly different compared with the contralateral healthy eyes.

Abbreviation: LS-HT, low spatial frequency -high temporal frequency (magnocellular pathway stimulated mode), HS-LT, high spatial frequency-low temporal frequency (parvocellular pathway stimulated mode).

(4) There was no significant difference of AL between amblyopic eyes and fellow eyes both in the AA and SA groups ($p > 0.05$), and there was also no significant correlation between axial length and OCT, P-ERG parameters (Pearson correlation test).

Discussion

Amblyopia occurs when there are abnormal visual experiences during the sensitive period of visual development, leading to the reduction of one or both eyes' BCVA to below age standard. In this study, we used OCT and P-ERG to investigate retinal structural and functional changes in adult patients with monocular anisometropic or strabismic amblyopia. The analysis of RNFL thickness comprised of four regions and P-ERG was recorded and analyzed by two different modes, biasing the parvocellular pathway and magnocellular pathway respectively. We found GCC and all sectors of RNFL thickness except the temporal sector significantly increased and P_{50} and N_{95} amplitudes significantly reduced in the amblyopic eyes of the AA group compared with the fellow eyes while no significant changes of OCT and ERG parameters could be seen in SA group.

Inconsistent results have been reported by different scholars in observing the changes of retinal structure in amblyopia by using OCT. Altintas [7] et al. and Al-Haddad et al. [8] found that the RNFL thickness of amblyopic eyes was not significantly different from the contralateral healthy eyes in either adult or children patients with anisometropic amblyopia. Furhtermore, Firat et al. [20] reported that RNFL thickness in the amblyopic eyes of children was not significantly different from the healthy eyes in the normal control group. But Yoon et al. [9] found that RNFL was significantly thicker in the amblyopic eyes than the contralateral healthy eyes in anisometropic amblyopic children. We speculated that the cause of the inconsistency was that the total peripapillary RNFL had been analyzed in previous studies whereas different regions of RNFL might vary in amblyopia. So we analyzed RNFL in four sectors separately in this study and found RNFL thickness in the nasal, superior and inferior sectors significantly increased. At the same time, the temporal sector of RNFL, where the maculopapillary bundle is located, in amblyopic eyes is thinner. The maculopapillary bundle is believed to be responsible for the central visual signals from the macula to the optic nerve. Previous studies suggested that in amblyopia, central vision is impaired; in other words, damage occurs mainly in the center of the macula and central visual pathways with no significant change to peripheral vision when compared to the contralateral eyes. We speculated that the thinning of RNFL in the maculopapillary bundle may cause degeneration of central vision and corresponding excessive ganglion cell atrophy or apoptosis. Thickening in RNFL layer in other sectors might be due to the blocking of normal ganglion cells' apoptosis after birth [10].

Changes in ganglion cells after birth are considered to be one of main reasons for retinal structural alteration in amblyopia [10]. Apart from RNFL, the GCC layer includes inner plexiform layers, ganglion cell body, and nerve fiber. Tugcu et al. [13], using OCT to measure GCC thickness, found that in strabismic amblyopia patients (aged 3–13 years), the GCC layer was thicker when compared to the fellow healthy eyes. However, Park et al. [12] found that patients with amblyopia had significantly reduced GCC layer average thickness than the contralateral healthy eyes. The present study found an increase in the thickness of the GCC layer in adult patients with anisometropic amblyopia compared with the contralateral eyes, but no statistically significant change in strabismic amblyopia. This is consistent with the study by Yen et al [10] that suggested that normal apoptosis of retinal ganglion cells was blocked after birth in amblyopia, which can lead to an increase in RNFL thickness. Szigeti A et al. [11] suggested that if Yen and others' hypothesis was correct, then the suppression of retinal ganglion cells' apoptosis

would not only affect the thickness of the RNFL, but also result in a thickening of the GCC layer. These studies provided evidence that the mean GCC thickness would increase in amblyopia.

Besides the structural changes that could be observed in the amblyopic eyes, P-ERG was used in exploring the functional changes of the retina in our study [25]. The P_{50} wave of P-ERG was suggested to reflect the function of retinal ganglion cells [26] while the N_{95} wave was believed to be a specific indicator of retinal ganglion cell function [27–28] and N_{95} amplitude reduction implied function defects of retinal ganglion cells. There were many studies on patients with amblyopia in P-ERG changes, but results still remained inconsistent. Tepping et al. [21], Guttob et al. [15] and Hess et al. [16] found no significant difference between amblyopic eyes and the normal control eyes in either amplitude or latency of P_{50} and N_{95}. Tugcu B et al. [13] and Arden et al. [14], using the same stimulation patterns, found that among patients with amblyopia, there were no significant differences in the amblyopic eyes' P-ERG latency compared to the fellow eyes, but P_{50} amplitude in the amblyopic eyes declined significantly when compared to the normal control eyes, indicating the decline of retinal ganglion cell function. Manny et al. [22], also under the same stimulation patterns, found that P_{50} amplitude decreased in amblyopic eyes compared to the contralateral healthy eyes and pointed out that this may be due to the amblyopic eyes' retinal ganglion cell function decline. In this study, we used a low temporal frequency - high spatial frequency mode (HSLT) and a high temporal frequency - low spatial frequency mode (ISHT) to respectively bias parvocellular pathway and magnocellular pathway. These two visual transmission pathways are relatively separated from the retina to LGN, anatomically and functionally [23, 24]. We found that both P_{50} and N_{95} wave amplitudes declined in patients with anisometropic amblyopia under the parvocellular pathway biased stimulation, while no magnocellular pathway impairments could be observed in anisometropic amblyopia. These results suggested that in the patients with anisometropic amblyopia, the damage might exist in some of retinal ganglion cells that were responsible for signal transmission of the parvocellular pathway.

Ganglion cell development requires the stimulus of a clear optical image [26]. In anisometropic amblyopia, the eyes' refractive state does not allow a clear image to be projected onto the retina. This may affect the normal development of the ganglion cells leading to structural and functional abnormalities, which may in turn affect the photoelectric signal conversion or signal transmission of the retina, resulting in amblyopia development. In strabismus amblyopia patients, neither GCC nor RNFL thickness was significantly different in the amblyopic eyes compared with the fellow eyes, and also no statistically significant difference existed in amplitude and latency of P_{50} and N_{95} when compared with the fellow eyes. Our results are consistent with the results of Altintas et al. [7] and Kee et al. [17]. These findings also support the hypothesis that the mechanism of anisometropic amblyopia is different from strabismic amblyopia. The visual pathway damage of strabismic amblyopia may be mainly in the visual cortex [29], and the retina may be as normal as the fellow normal eyes.

Since the present study enrolled subjects who were all over the age of 18, the confounding factor of age has been excluded in comparison with previous studies. Axial length was not corrected during analysis

because the authors did not find a significant difference between the amblyopic eyes and the fellow eyes in AL. No significant correlation between axial length and OCT, P-ERG indicators was established. These results are consistent with the findings of Szigeti A [11].

Conclusion

In this study, we found that in the amblyopic eyes in patients with anisometropic amblyopia, relative to the fellow healthy eyes, RNFL in the temporal sector was significantly thinner where the maculopapillary bundle is located, whereas RNFL thickness in the nasal, superior and inferior sectors was increased and the mean GCC layer was thickened as well. Functionally, P-ERG showed that the anisometropic amblyopia eyes had a reduction in the amplitude of P_{50} and N_{95} under the parvocellular pathway stimulated mode, indicating changes in the function of the retina in patients with anisometropic amblyopia was selective to parvocellular pathway. No statistically significant difference could be seen in OCT and ERG parameters among patients with strabismic amblyopia. These findings also supported the hypothesis that the pathological mechanisms were different between anisometropic and strabismic amblyopia. The visual pathway damage of strabismic amblyopia may be mainly in the visual cortex.

In this study, we have some limitations. As the participants in this research is relatively low, and because of the functional limitations of PERG, its hard to distinct the parvocellular pathway and the magnocellular pathway very exactly. So, in the future of our work,we may find some new way to distinct the two different pathways and include more cases.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Anhui Medical University and followed the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Consent to publish

Not applicable.

Availability of data and meterials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

We declare that we have no financial or personal relationships with other people or organizations that could inappropriately influence this work.

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Authors' Contributions

SL, YL, RL, JJ, WW: made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

GY, XP, CS, WH: been involved in drafting the manuscript or revising it critically for important intellectual content;

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Figures

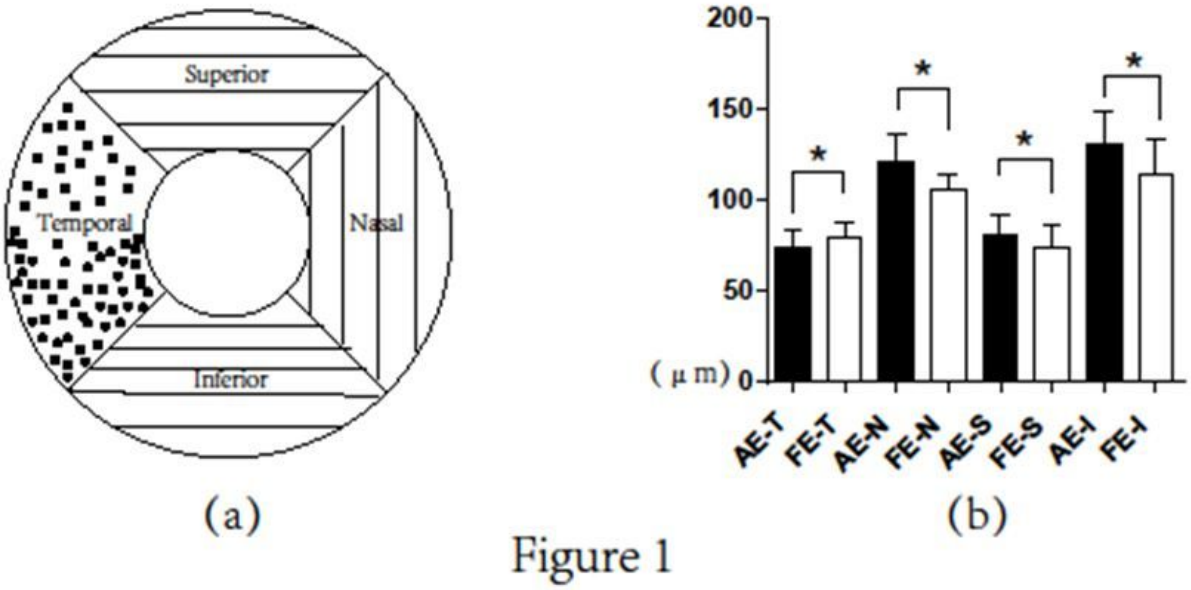

Figure 1

Figure 1

(a) : Schemata of amblyopic eyes' RNFL thickness in the AA group. The measurement area of RNFL thickness is separated into four sectors: Temporal (T), Superior (S), Nasal (N) and Inferior (I). The striped area represent the sectors in the amblyopic eyes where RNFL thickness is thicker than the contralateral healthy eye. The dotted area represent the sector in the amblyopic eyes where RNFL thickness is thinner than the contralateral healthy eyes. (b□□The RNFL thickness histogram of the amblyopic eyes and the fellow eyes in the AA group. The X axis represents the different sectors of the RNFL, with the solid column representing the amblyopic eyes (AE) and the hollow column representing the fellow eyes (FE). By a paired t-test, the asterisks indicate data with a statistically significant difference between the two groups. TL (t=-2.353, p=0.033); SN (t=3.970, p=0.001); NL (t=3.307, p=0.005); IN (t=5.573, p□0.001).

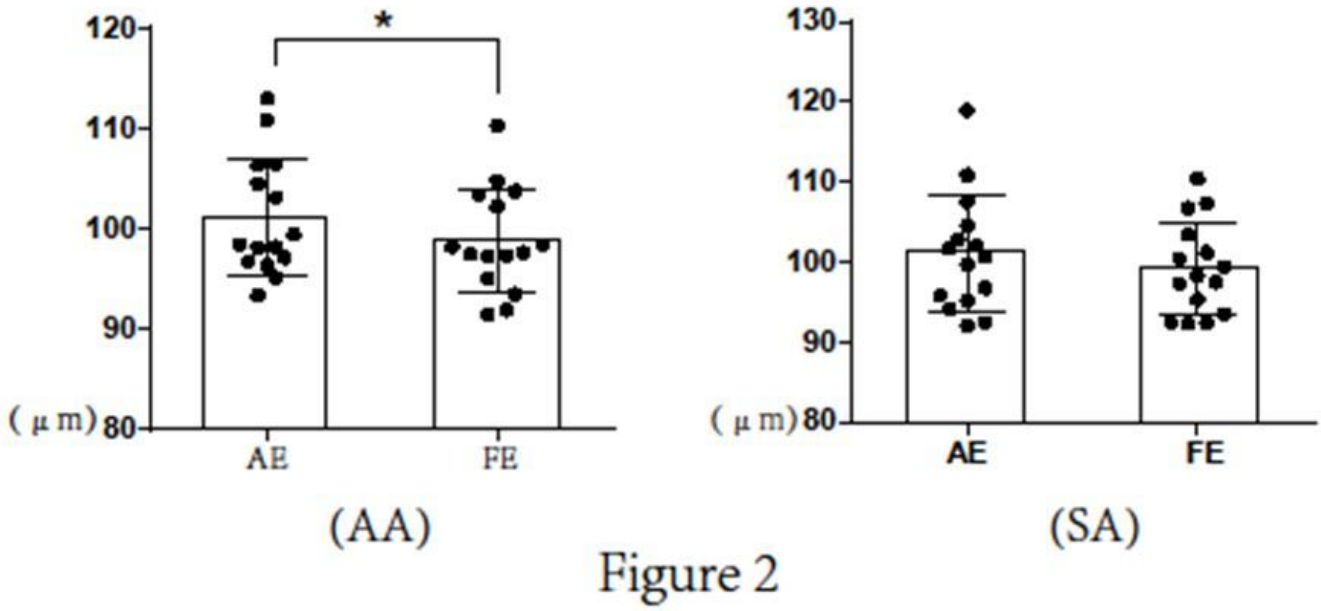

Figure 2

Figure 2

GCC thickness within the 6 mm diameter range surrounding the fovea With the AE and FE represented on the X axis. The Y axis represents the GCC thickness (with error bars). The scatter dots represent all data from the sample. The asterisk shows the significantly statistical difference between the two groups. AA: GCC thickness in AA patients; SA: GCC thickness in SA patients. By a paired t test, amblyopic eyes' GCC thickness is thicker than that FE（n=15,t=2.264，p=0.039）in the AA group，but in the SA group, there was no statistically significant difference between two eyes.