

# Mydriasis-Free Flicker Electroretinograms in 204 Healthy Children Aged 0–18 Years: Reference Data From Two Cohorts

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**Purpose:** The purpose of this study was to summarize the flicker electroretinogram responses (ERGs) in healthy children using RETeval, a small handheld mydriasis-free full-field flicker ERG system.

**Methods:** Flicker ERGs were recorded with the use of the RETeval system in 204 healthy children (aged 18 years and below) from 2 countries, China and the United States. The effects on ERG measurements of the subject's demographics and location were analyzed.

**Results:** The implicit times have no correlation with the population (China cohort and US cohort), sex, and refractive error. In contrast, the amplitudes were dependent on demographics. The amplitude differences were small compared to the 95% reference interval; therefore, a single (age-corrected) reference interval can be used in both locations and both sexes. The implicit times and amplitudes mature over the first decade of life with exponential time constants of 2.5 years and 4.1 years, respectively, whereas most of the trend is within the first 6 years (implicit times) and 9 years (amplitudes).

**Conclusions:** The age dependence and percentiles obtained in this study could serve as reference data against which the ERG responses from pediatric patients can be compared.

**Translational Relevance:** The flicker ERG is one of the standard methods for the assessment and diagnosis of vision-related disorders. This study provides reference data in pediatric subjects, which can then be used to aid in the interpretation of flicker ERG results.

## Introduction

Full-field electroretinography is a basic clinical test that is used to evaluate the retinal function in healthy subjects and patients with various types of retinal diseases. The flicker electroretinograms (ERG) is one of the standard methods for the assessment and diagnosis of retinal diseases.<sup>1</sup> The flicker ERGs are elicited by intermittent stimulation at a frequency of about 30 Hz. As the rods do not respond to such high frequencies, flicker ERGs are considered cone-mediated responses.

There are several reasons why the flicker ERGs serve as an ideal diagnostic screening tool in children.<sup>2–4</sup> First, the majority of nystagmus-inducing retinal disorders of infancy and young childhood, including achromatopsia and Leber congenital amaurosis, involve the cones. Second, flicker recording is usually performed very quickly, requires no dark adaptation, and can be performed in a patient previously exposed to typical room light. Finally, the cone flicker response is obtained by averaging many responses over a short period of time, resulting in an increased signal-to-noise ratio with high reproducibility.

However, the flicker ERG has not been widely used in pediatric patients with retinal diseases for the following reasons: a large space is required for the conventional ERG recording devices, there is a need for mydriasis and topical anesthesia, and the placement of the electrodes on the cornea or conjunctiva requires specific expertise.<sup>5-9</sup> Recently, a full-field flicker ERG recording system, known as the RETeval system, was developed.<sup>10-12</sup> This system consists of a small handheld ganzfeld dome with a special single-use skin electrode array; thus, there are no electrodes on the cornea or the conjunctiva. This system can record flicker ERGs without mydriasis because the device delivers stimulus flashes with constant retinal illuminance, thereby limiting the total testing time to less than 1 minute.

Given the potential benefit for a portable, nonseated, less time-consuming, efficient cone flicker ERG evaluation in low-risk children, the RETeval flicker ERG is considered as a powerful tool for detecting pediatric ocular diseases, especially in the identification of hereditary retinal disorders,<sup>3</sup> for which early diagnosis is becoming more important as effective gene therapies are being developed. However, the system manufacturer has not yet provided reference data applicable for the younger population, which would improve its diagnostic utility in this population.

Thus, the purpose of this study was to determine the factors affecting the implicit time and amplitude of flicker ERG in children aged 18 years and below and to establish the reference data of flicker ERG in healthy children.

## Methods

### Study Design

This was a prospective study conducted at one site in China between 2017 and 2019. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Zhongshan Ophthalmic Center (2020KYPJ112), Sun Yat-sen University. Informed consent was obtained from the parents of all participants. In addition, data from healthy subjects in the RETeval All Comers Trial (REACT), ClinicalTrials.gov Identifier NCT03065881, was used courtesy of Quentin Davis from LKC Technologies, Inc. The REACT trial was performed at six trial sites across the United States.

### Subjects

Children whose age ranged from 0 to 18 years were recruited. Those who had any known ocular or

systemic diseases or myopia of  $-3.0$  diopters (D) or more were excluded. The inclusion criteria included the following: (1) all infants and children born at term ( $40 \pm 2$  weeks) gestation, (2) best-corrected visual acuity (BCVA) of at least 20/25 Snellen visual acuity in children older than 3 years of age, no requirement for BCVA in the children younger than 3 years old, (3) IOP  $\leq 20$  mm Hg, (4) optic nerve cupping  $< 50\%$ , and (5) refractive error (spherical equivalent) between  $-3.0$  D and  $+3.0$  D. All patients underwent a comprehensive ophthalmic examination, including slit-lamp examination, refractive error (spherical equivalent) by autorefractometry (KR-800; Topcon, Tokyo, Japan), BCVA, and wide-field funduscopy with Retcam3 (Clarity Medical Systems, Inc., Pleasanton, CA, USA) in children under 3 years old or scanning laser ophthalmoscopy (Daytona, United Kingdom) in children 3 years old and above. Spectral domain-optical coherence tomography (SD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA, USA) was used to confirm the normal macular microstructure. The axial length was obtained but not analyzed because of its strong collinearity with the refractive error. The REACT inclusion criteria were similar, with the exception that term births were not required.

### RETeval Flicker Electroretinography

All subjects were tested with natural pupils, no artificial dilation. Full-field flicker ERGs were recorded using the RETeval system (LKC Technologies, Gaithersburg, MD, USA). The specifications of the device have been described previously.<sup>13,14</sup> LKC Skin Sensor Strips were used. International Society for Clinical Electrophysiology of Vision (ISCEV) standard flicker parameters were followed, which consist of a 85 Td-seconds of white light flash (28.3 Hz) and a 848 Td white background.<sup>15</sup>

The peak-to-peak amplitude and waveform implicit time are reported. These values are automatically measured and displayed by the RETeval system.<sup>16</sup> The majority of children ( $n = 190$ ) were sufficiently compliant to undertake the RETeval recording. Oral sedation (chloral hydrate 75 mg/kg) was administered in 14 children (14/204, 6.9%) to complete the comprehensive testing.

### Statistical Analysis

Analyses were performed using Mathematica Version 12.3 (Wolfram Research, Champaign, IL, USA). Following Davis and Hamilton,<sup>17</sup> data from both eyes are used for the analysis. The results from one eye was missing in 38 individuals; these results were

duplicated so that each subject had 2 results. Whereas using data from both eyes (and the duplicated points) does involve using correlated data ( $r^2 = 0.92$  for times and  $r^2 = 0.72$  for amplitudes between eyes for subjects with data from both eyes), there is still information present due to the lack of perfect correlation. If replicates were available, only the first measurement was used so as to not inappropriately reduce device-related variability during the construction of reference intervals.

The 30 Hz flicker ERG implicit times and amplitudes were compared between populations and sexes using the Mann-Whitney  $U$  test, after non-normative distribution was confirmed for most of the datasets using the Shapiro-Wilk normality test. The age-dependence of the ERG was computed using robust nonlinear curve fitting methods having three terms: a constant term, a decaying exponential representing the maturation of the eye, and a linear term representing the slow change of the ERG with age after maturation. All subjects were used in the age fit. Residuals, which are differences between measurements and the fit, were computed. The residuals did not show an age dependence, so percentiles were computed on the residuals, which are then added back to the fits to form age-dependent reference intervals.<sup>17</sup> The results were considered statistically significant when the  $P$  value was less than 0.05.

## Results

### Demographic Characteristics of the 204 Healthy Children

A total of 204 healthy subjects, including 153 children from China and 51 children from the United States were included in the study. The median age of the subjects was 9 years, with a range of 4 months to 18 years. Eighty-one (39%) children were under 7 years old, 7 (3.4%) children were less than 1 year old. No children were less than 1 month old. There were 73 Chinese girls, 80 Chinese boys, 30 American girls, and 21 American boys. Of the 51 Americans, 41 were White, 4 were Black, 5 were Pacific Islanders, and 1 was mixed races. The two study locations, China and the United States, are effectively different racial groups in addition to differing in location. In total, 101 children were boys, and the ratio of male to female children was 0.98:1. In the China group, the mean refractive error (spherical equivalent) was  $-1.05 \pm -1.04$  D (range =  $-3.0$ D to  $+3.0$  D), and there was no difference in myopia between the sexes. Only 14 (25.5%) of the 55 children under 5 years old required sedation.

### Comparison Between Chinese versus US Cohort Populations

In our study, the majority of the US cohort participants were aged 9 to 18 years old. Thus, the comparison was performed between age-matched China (9–18 years old, 47 eyes) and the United States (9–18 years old, 51 subjects) childhood cohorts. The average implicit time had a median of 24.5 ms with a range of 23.3 to 27.1 ms in China children, whereas the median was 24.7 ms with a range of 23.3 to 27.1 ms in US children. There was no statistical difference observed ( $P = 0.21$ ). However, the average amplitude was lower in China children with a median of 28.4  $\mu$ V (range = 17.6–46.7  $\mu$ V) than that in US children with a median of 31.5  $\mu$ V (range = 19.4–54.7  $\mu$ V,  $P < 0.001$ ).

An ANOVA test with Bonferroni correction was additionally performed and demonstrated that largest effect size was 7.5  $\mu$ V between demographic variables, which is 22% of the size of the 95% reference interval. This difference is sufficiently small that partitioning the reference data is not required.<sup>17</sup>

### Comparison of Implicit Times and Amplitudes in Flicker ERG by Sex

There were no statistically significant differences in the flicker ERG with sex. The median implicit time was 25.0 ms (range = 23.3 ms–33.2 ms) in boys and 24.7 ms (range = 23.2 ms–31.1 ms) in girls ( $P = 0.378$ ; Fig. 1A). Moreover, the amplitude in boys (median = 27.2  $\mu$ V, range = 9.9–54.7  $\mu$ V) and girls (median = 28.8  $\mu$ V, range = 8.7–54.1  $\mu$ V) was also similar ( $P = 0.384$ ; Fig. 1B).

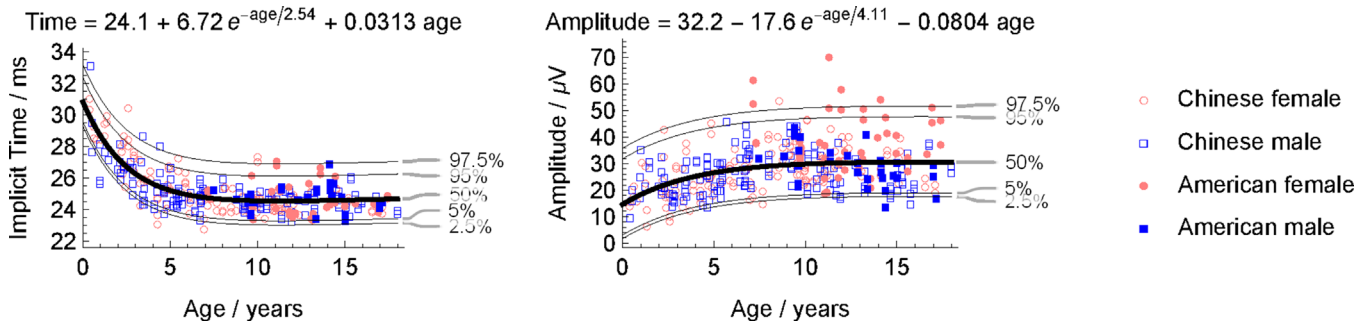
### Regression Analysis Between Implicit Time in Flicker ERG and Age

A loess regression best fit to the data is shown (see Fig. 1A). The best-fit equation is:

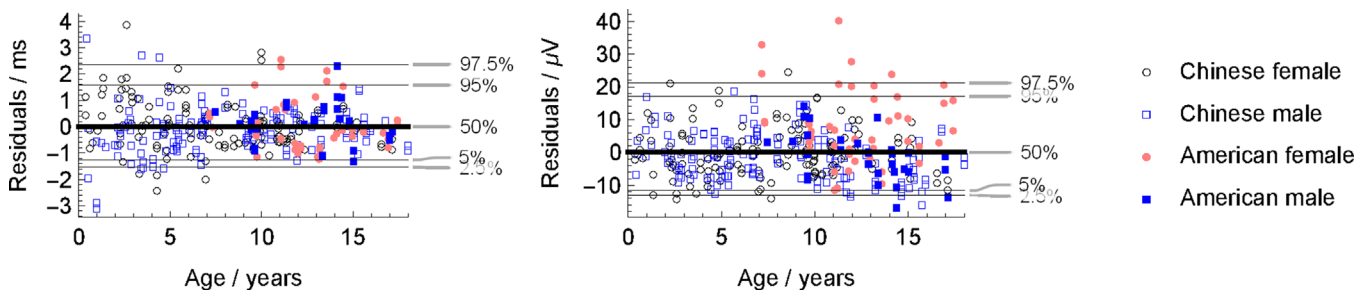
$$\text{Implicit time} = 24.1 + 6.72 e^{-\text{age}/2.54} + 0.0313 \text{ age}$$

Where the implicit time is in units of ms, age is in units of years, and  $e$  is Euler's number (2.71828...). Based on this equation, the expected implicit time at birth is 24.1 ms + 6.72 ms = 30.8 ms. The residuals versus age are shown in Figure 2A. As can be seen, there is no significant trend in the mean across age, indicating a good fit.

The flicker time gets faster exponentially with a 2.5 year time constant, down to a time of 24.5 ms at age 11 years (although most of the downward trend is done by age 6 years, about 2.3 time constants).



**Figure 1. Flicker ERG dependence on age.** Flicker implicit time (A) and amplitude (B) are shown versus age. Female patients are shown in red, male patients are shown in blue, Chinese patients are shown with open symbols, and American patients are shown with filled symbols. There is one symbol per patient per eye. The fit equation for the dark curve (labeled 50th percentile) is shown in the top of the plot. Other percentiles with additive offsets are shown with thin black lines.



**Figure 2. Fit residuals of regression ERG dependence on age.** The fit residuals, or the difference between the measurements and the fit equation are shown for the implicit time (A) and amplitude (B). Female patients are shown in red, male patients are shown in blue, Chinese patients are shown with open symbols, and American patients are shown with filled symbols. There is one symbol per patient per eye.

Afterward, the flicker time slowly gets longer at a rate of 0.3 ms/decade.

### Regression Analysis Between Amplitude in Flicker ERG and Age

The best-fit equation for amplitudes (see Fig 1 B) is

$$\text{Amplitude} = 32.2 - 17.6 e^{-\text{age}/4.11} - 0.0804 \text{ age}$$

Where the amplitude is in units of  $\mu\text{V}$ , age is in units of years, and  $e$  is Euler’s number (2.71828...). Based on this equation, the expected amplitude at birth is  $32.2 \mu\text{V}$  to  $17.6 \mu\text{V} = 14.6 \mu\text{V}$ . The residuals versus age are shown in Figure 2B. As can be seen, there is no significant trend in the mean across age, indicating a good fit.

The amplitude gets larger exponentially with a 4.1 year time constant, up to an amplitude of  $31 \mu\text{V}$  at age 16 (although most of the downward trend is done by age 9, about 2.3 time constants). Afterward, the amplitude slowly gets smaller at a rate of  $0.8 \mu\text{V}/\text{decade}$ .

### Suggested Reference Data of Implicit Time and Amplitude of the Flicker ERG in Children

As seen in Figures 2A and 2B, the scatter in the residuals for both time and amplitude are similar across ages. Therefore, all the data can be combined to compute percentiles which can then be added back to the age-dependent fits.<sup>17</sup> The percentiles needed for 95% reference intervals (both 1 and 2 tailed) are shown

**Table 1.** Additive Component to Calculate Reference Percentiles

Quantile	Additive Amount for	
	Implicit Time (in ms)	Amplitude (in $\mu\text{V}$ )
0%	-3	-19
1%	-1.9	-15
2.5%	-1.6	-13
5%	-1.4	-12
95%	1.9	17
97.5%	2.9	21
99%	3.7	28
100%	4.1	40

**Table 2.** Percentiles for RETeval Cone Flicker Response According to Equation From Regression Line

Age	Implicit Time (in ms)					Amplitude (in $\mu$ V)					Total (Males: Females)	
	Lower Range (0%)	5.0%	50%	95.0%	Upper Range (100%)	Lower Range (0%)	5.0%	50%	95.0%	Upper Range (100%)	China 153 (80:73)	United States 51 (7:10)
1	25.66	27.26	28.66	30.56	32.76	-0.68	6.32	18.32	35.32	58.32	7 (4:3)	—
2	24.22	25.82	27.22	29.12	31.32	2.22	9.22	21.22	38.22	61.22	6 (1:1)	—
3	23.26	24.86	26.26	28.16	30.36	4.48	11.48	23.48	40.48	63.48	16 (1:1)	—
4	22.62	24.22	25.62	27.52	29.72	6.23	13.23	25.23	42.23	65.23	11 (5:6)	—
5	22.20	23.80	25.20	27.10	29.30	7.58	14.58	26.58	43.58	66.58	15 (8:7)	—
6	21.92	23.52	24.92	26.82	29.02	8.63	15.63	27.63	44.63	67.63	11 (8:3)	—
7	21.75	23.35	24.75	26.65	28.85	9.43	16.43	28.43	45.43	68.43	15 (2:1)	3 (1:2)
8	21.64	23.24	24.64	26.54	28.74	10.04	17.04	29.04	46.04	69.04	4 (1:3)	1 (1:0)
9	21.58	23.18	24.58	26.48	28.68	10.51	17.51	29.51	46.51	69.51	7 (3:4)	8 (1:1)
10	21.54	23.14	24.54	26.44	28.64	10.85	17.85	29.85	46.85	69.85	14 (2:5)	1 (0:1)
11	21.53	23.13	24.53	26.43	28.63	11.10	18.10	30.10	47.10	70.10	13 (5:8)	8 (1:7)
12	21.54	23.14	24.54	26.44	28.64	11.29	18.29	30.29	47.29	70.29	10 (7:3)	4 (1:1)
13	21.55	23.15	24.55	26.45	28.65	11.41	18.41	30.41	47.41	70.41	5 (2:3)	7 (2:5)
14	21.57	23.17	24.57	26.47	28.67	11.49	18.49	30.49	47.49	70.49	3 (2:1)	8 (1:1)
15	21.59	23.19	24.59	26.49	28.69	11.54	18.54	30.54	47.54	70.54	4 (1:1)	2 (1:1)
16	21.61	23.21	24.61	26.51	28.71	11.55	18.55	30.55	47.55	70.55	8 (3:1)	3 (1:2)
17	21.64	23.24	24.64	26.54	28.74	11.55	18.55	30.55	47.55	70.55	2 (1:1)	2 (1:1)
18	21.67	23.27	24.67	26.57	28.77	11.53	18.53	30.53	47.53	70.53	2 (1:1)	4 (3:1)

in Figure 1. The amounts to be added to reach a certain percentile are shown in Table 1.

For example, the 95% 2-tailed reference interval for implicit times is 2.9 ms to (-1.6 ms) = 4.5 ms wide. At age 2 years, this interval is  $24.1 + 6.72 e^{-2/2.54} + 0.0313 \times 2 - 1.6$  to be  $24.1 + 6.72 e^{-2/2.54} + 0.0313 \times 2 + 2.9$ , or 25.6 ms to 30.1 ms. More commonly, 1-tailed reference intervals are appropriate for flicker ERG measurements; therefore, any time faster than  $24.1 + 6.72 e^{-2/2.54} + 0.0313 \times 2 + 1.9 = 29.1$  ms would be considered consistent with a 2-year-old child with normal vision. For more convenient use, a look-up table with the reference data and the 95% percentiles is shown in Table 2.

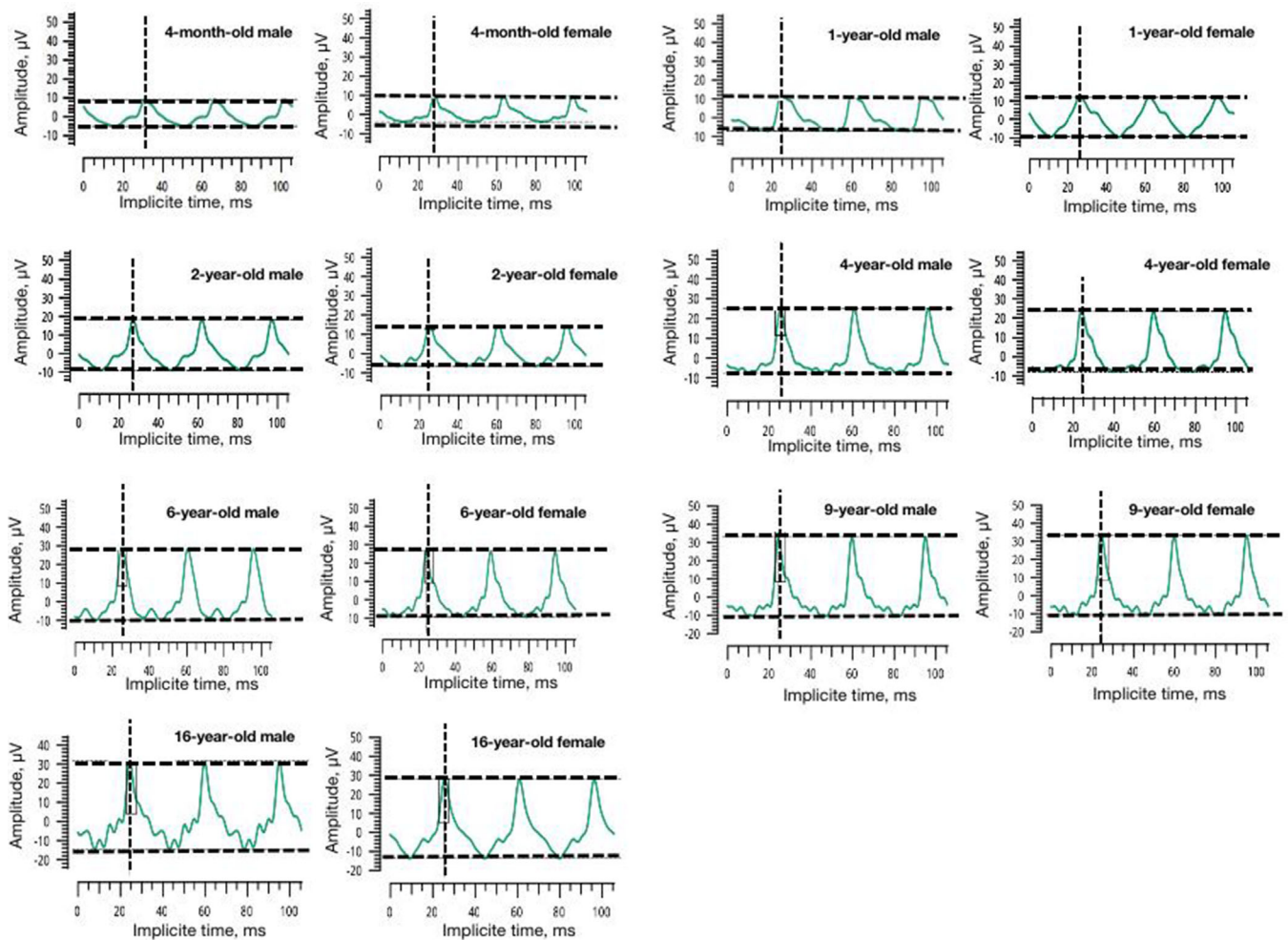
Representative waveforms of flicker ERGs recorded from 6 eyes of 5 children aged 4 months to 18 years old are illustrated in Figure 3.

## Discussion

Electroretinographic testing is essential in establishing diagnosis in infants and children with visual impairment; however, conventional ISCEV full-field ERG is time-consuming and requires sedation in children. To our knowledge, there are very limited data on full-field ERG in young children. Thus, four studies<sup>15,18-20</sup> focused on ERG testing in children younger than 3 years old, and sedatives were used in 3 of them. For instance, in Boese’s study, 56% of children under 8 years old required sedation for the full-field ERG test.<sup>19</sup> Sometimes, the protocol had to be customized

to increase compliance among nonsedated younger children, for example, reducing the light adaption time to 3 minutes instead of 10 minutes, as recommended by the ISCEV. In our study, the majority of younger children were sedation-free. According to age, only 15.6% (14/90) of children under 8 years old, 25.5% (14/55) under 5 years old, and 51.9% (14/27) under 3 years old were sedated with chloral hydrate to complete the RETeval standard full-field ERG assessment (only flicker ERG was analyzed in the current study), which obviously yielded better compliance than that of prior similar studies. The major advantages of this procedure include the following: (1) it is noninvasive, using only skin electrodes, and (2) it is time efficient in terms of the procedure preparation and execution, with a short total recording time and without the need for mydriasis. This makes the portable ERG device a feasible, fast, and effective tool in the everyday clinical practice of a pediatric ophthalmologist, particularly in examining preschool and school children.

The factors influencing the results of flicker ERG are still unclear, and the association between sex and amplitude remains controversial. Kato et al.<sup>21</sup> showed that using the same RETeval device for measurement, women in their 20s were independently associated with larger-amplitude fundamental components of the flicker ERGs (no change in fundamental timing) compared to age-matched men, although the reason is unknown. Grace et al.<sup>15</sup> noted shorter fundamental implicit times in female patients than those in male patients (0.9 ms,  $P = 0.04$ ) in a small sample size of normal subjects including 18 male patients and 13 female patients; however, the trend of larger



**Figure 3. Representative flicker ERG in Children with different age.** Representative flicker ERGs of the right eye are shown for a 4-month-old infant (A), 1 year (B), 2 years (C), 4 years (D), 6 years (E), 9 years (F), and 16 (G) year old healthy children. The implicit times for each age group from male to female patients were 31.1, 27.8, 25.7, 26.6, 26.4, 24.8, 26.9, 24.1, 26.8, 24.6, 24.9, 24.6, 24.9, and 25.8 ms, respectively, and the amplitudes were noted as 14.3, 16.1, 15.9, 20.8, 27.6, 21.7, 33.0, 32.1, 38.5, 43.7, 45.6, 38.8, and 41.2  $\mu$ V.

fundamental amplitudes among female patients was nonsignificant. In current study, we investigated the effect of sex on the flicker ERG response with a cohort of larger sample size. Although implicit times did not vary among groups, amplitudes were significantly larger in female patients (2.6  $\mu$ V), and larger still in the American female cohort (7.5  $\mu$ V). We found in China that young female children were more often cooperative with testing than young male children, which may be a contributory factor.

Interestingly, US children tended to have a larger amplitude than Chinese children, although the implicit time was similar. The cause of the disparity has not yet been determined. One possible biological explanation is the two cohorts consisted of different races, and there is a genetic component to ERG flicker ampli-

tudes.<sup>22</sup> Another possible explanation is methodological: the ERG amplitude (but not timing) is dependent on Sensor Strip electrode positioning,<sup>22</sup> and there might have been systematic placement differences by the device operators in the locations. Nevertheless, the differences are sufficiently small compared to the 95% reference interval that partitioning is not required.<sup>17</sup>

To date, the normal ranges of ERG responses from infancy to childhood remain incompletely defined in terms of conditions commonly occurring in the clinical setting; thus, it is crucial to establish the reference data for RETeval flicker ERG in children, especially in younger children less than 5 years old. It is well known that infants have significant immaturities of retinal processes and their ERG responses are lesser than those of adults. Several studies showed a trend of

gradual cone flicker maturation in early childhood with ISCEV standard setting. However, recently, Grace et al. found that age had no effect on the RETeval cone flicker amplitudes and implicit times in a small cohort of normal healthy children.<sup>15</sup> In Kato's study, in which only young adults in their 30s were included, the age showed fair correlation ( $r < 0.2$ ) with the amplitude of flicker ERG.<sup>21</sup>

The most important finding in the current study is that of the precise determination of how implicit time and amplitude vary with age. With a cohort of more than 200 healthy children, we found that both timing and amplitude maturation is well-fit by exponential functions, respectively. Using these formulae, reference intervals can be generated for any age (less than 19 years). Based on the form of the equation, we expect that it will be a useful model for adult subjects as well.

The underlying reason for the changes in the results of flicker ERGs in younger children has not yet been determined. According to the limited studies on reference ERG data in children, it is presumed that cone responses mature earlier than those of rods and that in recordings in children,<sup>18,23,24</sup> a full-field flicker ERG response predominantly represents the function of the peripheral cone system, as central cones only account for about 1% of the total number of cones. Therefore, we believe that the function of cones increases and matures with visual development over the first decade of life. In addition to cone maturation, the postsynaptic pathways of the cone system that dominate the flicker ERG response<sup>24,25</sup> must also be maturing in the first decade of life.

There are several limitations to this study. First, there are two ways to measure flicker results, either examining the whole waveform or just the fundamental component of the Fourier transform of the results. Whereas the RETeval device shows both types of results, here, we only examined only the waveform results. Second, the Sensor Strip skin electrodes used by the RETeval system were designed for older children and adults. Their large size made them difficult to position on an infant's face. As a result, the electrodes probably did not adhere completely to the skin underneath the eyelids. Thus, the underestimation of amplitude levels is possible. Third, in this study, the pupillary area was recorded but was not analyzed. Although the pupillary area was found as an independent factor of implicit time in flicker ERG by Kato et al.<sup>15</sup>

In conclusion, regression analyses of the results of the RETeval flicker ERGs of 204 healthy children showed that the age is an independent factor of flicker ERG, maturing over the first decade of life. Age should be considered carefully in the analysis of flicker ERG.

The age dependence and percentiles obtained in this study could serve as reference data against which pediatric ERG results can be compared.

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\* TZ and JL contributed equally to this work.

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