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Paediatric norms for photopic electroretinogram testing based on a large cohort of Chinese preschool children

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ABSTRACT

Objective Full-field electroretinogram (ffERG) is an objective test to determine the electroretinal activities in response to light stimulation for investigating retinal physiology and diagnosing retinal diseases. This study aimed to establish a reference data set of photopic electroretinogram (ERG) of Chinese preschool children in Hong Kong to facilitate clinical and research studies.

Methods and analysis Preschool children aged 3–7 years with normal vision were recruited from local kindergartens. Eye examinations, including cycloplegic spherical equivalent refraction (SER), axial length (AL) and keratometry (K) measurements, were performed. ffERGs of the International Society for Clinical Electrophysiology of Vision (ISCEV) standard photopic flash and 30-Hz flicker protocols were measured using RETeval with Sensor Strip skin electrodes. ERG waveform characteristics were extracted, and relationships between ERG, age, SER, AL and K were evaluated.

Results A total of 479 children completed the measurements (mean age: 5.0±0.9 years, 45.5% female). Mean, 95% CIs, 5th–95th percentile range of the ERG parameters were reported. Age was positively associated with amplitudes of b-wave and 30-Hz flicker (p<0.01), but negatively associated with implicit times of b-wave and 30-Hz flicker (p<0.01). AL was significantly associated with all amplitudes of a-wave, b-wave and 30-Hz flicker (p≤0.01) and implicit time of both a-wave and 30-Hz flicker (p<0.05). K was positively associated only with 30-Hz flicker amplitude (p=0.01), and no association between all responses and SER.

Conclusion Reference data set of photopic ERG of Chinese preschool children was established. Cross-sectional investigations revealed associations between ERG, age, SER and AL, which were speculated to further implicate the role of retina in refractive error development.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The current available reference data sets of full-field electroretinogram (ffERG) using RETeval, a handheld non-mydriatic electroretinogram device, were limited by small sample sizes with wide age ranges.

WHAT THIS STUDY ADDS

⇒ This study established a specific reference data set of photopic ffERG for a large sample of Chinese preschool children using RETeval.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This normative reference data set of ffERG from paediatrics can be used in clinical applications and future studies on paediatric retinal physiological development.

INTRODUCTION

Paediatric ophthalmic assessment is essential to identify risk factors for ocular disease, determine the health condition of the eyes and monitor visual system development throughout childhood. It is important to rule out any visual impairment, which has been reported to affect almost 7% of children.[1] Regular ophthalmic examination, which includes the assessment of vision and evaluation of ocular health, can help reduce vision impairment. Young children's eyes under emmetropisation, which is an ocular developmental process, matches the eye's power and axial length (AL) to achieve clear vision at distance without accommodation, and the target outcome is no refractive error in the adulthood.[2] Visual acuity (VA) and refractive error measurements identify decreased vision caused by uncorrected refractive errors, which contribute to around 69% of childhood visual impairment in US children aged 3–5 years, but is also the most easily corrected visual problem.[3] Evaluation of ocular health helps to minimise the presence of ocular diseases, such as congenital cataract and optic nerve and retinal disorders, which were other commonly reported causes of visual impairment in children.[1] Comprehensive eye examinations and other additional tests are even more important for children with a family history of hereditary ocular diseases, such as congenital dystrophies, retinitis pigmentosa, and so on. However, such ophthalmic assessments are often difficult to

perform due to a lack of attention span and cooperativeness. Objective and standardised assessments are good choices to be performed in paediatrics.

Electroretinogram (ERG) is an objective functional test measuring the electrical properties of retinal cells in response to light stimulation. Full-field ERG (ffERG) measures the overall retinal response by stimulating the whole visual field with a homogenous flash. Conventional ffERG measurement requires mydriasis to standardise the amount of light delivered onto the retina.[4] A comprehensive ERG assesses the functions of the rod-mediated pathway in scotopic condition of a dark-adapted eye and the cone-mediated pathway in photopic condition of a light-adapted eye.[5] In a typical photopic flash ERG waveform, a negative a-wave reflecting photoreceptor physiology and a b-wave originating from cone ON-bipolar cells and Müller cells can be identified. There is a high frequency and relatively low amplitude component on the rising limb of b-wave termed oscillatory potentials, which reflects the inner retinal activities from amacrine cells and retinal ganglion cells.[5] A flash ERG also contains a photopic negative response, which is a slow negative component observed originating from the retinal ganglion cells after the b-wave in a brief-flash photopic (cone) ERG.[6] When the eye is stimulated with continuous flashes, that is, flicker, the generated ERG responses have been reported to be mainly attributable to postreceptoral neurons, representing the response of rapidly recovering cones.[7]

Retinal function is linked with children's developmental visual changes and may explain their visual behaviour, while ERG can objectively measure the physiological properties of retinal cells.[8] Although ERG has various clinical and research applications, it is difficult to perform conventional ERG with mydriasis in very young children due to inadequate cooperation and short attention span. For some infants and toddlers, general anaesthesia or sedation, which would affect the ERG results, may also be needed. Andréasson compared the ffERG results obtained in normal children with general anaesthesia and those with topical anaesthesia, and revealed reduced b-wave amplitudes and increased cone b-wave implicit time in the former group.[9] Sedation was also found to result in a reduction of scotopic a-wave and b-wave amplitudes, and anaesthesia caused a reduction in scotopic b-wave amplitude, photopic response amplitudes and a delay in implicit time of photopic responses.[10] Due to the difficulties in performing conventional ERG measurements in young children, there is a lack of large-scaled paediatric ERG normative data.

To tackle these shortcomings of conventional ERG, a commercial handheld portable ERG device (RETeval) has been developed, which allows easier measurements, particularly in preschool children. It comes with skin electrodes, which minimise the discomfort produced by electrodes in touch with the cornea. In addition, mydriasis may not be necessary because of the real-time pupillometric adjustment for pupil size in maintaining the optimal intensity of the retinal illuminance from the flash stimulus. It can conduct ERG measurements on children more comfortably without sedation or anaesthetics. The measurement time is also shorter than that of conventional ERG measurements. Thus, it is a useful tool to establish a set of normative data to evaluate retinal physiology and functions of paediatrics, especially for diagnosis of congenital retinal diseases.

ERG is not only ideal for diagnosing retinal diseases, but also a useful research tool to evaluate retinal physiology. For instance, ERG was found associated with refractive error and AL. Reductions in both scotopic and photopic a-wave and b-wave amplitudes and 30-Hz flicker amplitude were reported in adult subjects with more myopic refraction or longer ALs.[11 12] Chia et al longitudinally investigated the scotopic and photopic responses of myopic children aged 8–12 years and reductions in photopic a-waves and b-waves and 30-Hz flicker responses were observed while scotopic responses were less affected.[13] The relationship between ERG responses and age had also been investigated in previous studies but with no conclusive results.[14 15] There are also no definitive results of age effect on ERG response in previous studies.[16–18]

Several studies have reported the development of reference normative values of ERG responses with RETeval of both healthy subjects and diseased patients.[17–20] However, the sample sizes in these studies were relatively small and the age ranges were also quite wide, reducing the representativeness of the data for preschool children. Therefore, this study aimed to establish a reference data set for Chinese preschool children in Hong Kong using this handheld ERG device, which would be useful for future studies on paediatric retinal physiological development.

MATERIALS AND METHODS
Subjects
All healthy preschool children aged 3–7 years attending 11 local kindergartens identified by convenience sampling were invited to participate in the study. Written informed consent was obtained from parents/guardians of all subjects. Patients or the public were not involved in the design, conduct, or reporting, or dissemination plans of our research. Subjects underwent ophthalmic evaluations, including habitual VA measurement, electroretinography and ocular biometric measurements. Habitual VA was measured using an ETDRS chart with LEA symbols. Subjects with habitual VA worse than logMAR 0.3 were excluded from the study. Subjects with any known ocular diseases were also excluded from the analysis.

ERG measurement
The ffERGs were performed without mydriasis using a RETeval (LKC Technologies, USA) device with Sensor Strip skin electrodes. The RETeval device covers the eye with a Ganzfeld dome which allows a homogenous light stimulation to the whole retina during the measurement.

The skin electrodes were placed 2 mm below the lower eyelid margin of each eye with the end of the strip aligned with the centre of the pupil at the primary gaze. ISCEV standard photopic flash and flicker protocols were adopted to record the light-adapted cone responses from both eyes monocularly, consist of 85 Td/s white flashes delivered at 2 and 28.3 Hz, respectively, under white background of 850 Td.[21] The 28.3 Hz was within the tolerance of the ISCEV standard of 30 Hz flickering frequency. Subjects stayed in a well-illuminated room (about 300 lx) for at least 10 min of light adaptation before the ffERG recording. They were instructed to fixate on a central red light inside the Ganzfeld stimulator. Fixation stability was monitored simultaneously by viewing the built-in infrared eye/pupil tracking camera of the device. To ensure quality recordings, if the electrode noise exceeded 55 µV for single-flash tests or 5600 µV for flicker tests, the device would display a warning and the problem would be resolved before recommencing the measurement. Each ERG measurement lasted 5–10 min with breaks in between, while the subjects were allowed to leave both eyes open and uncovered according to the guideline from RETeval user manual to obtain better fixation. Data for analysis were obtained from a random eye.

Refractive error and biometric measurements
Cycloplegic objective refraction was performed using an open-field autorefractor (NVision K5001, Shin-Nippon, Japan) 30 min after instilling 2 drops of 1% cyclopentolate at a 5-min interval. The spherical power, cylindrical power and axis were determined by measuring five consecutive readings and taking the representative value automatically generated by the autorefractor. Readings beyond 0.50 D were removed and retaken.[22] The refraction reading was then reported as spherical equivalent refraction (SER) by the following equation: spherical power + ½cylindrical power. Ocular biometric measurements, including AL and keratometry (K) (represented by the mean corneal curvature of steep and flat meridians), were measured using an optical biometer (Aladdin, Topcon Corp., Japan). The equipment was positioned at where an appearance of a 'green eye' quality control image was present, which indicated a working distance of approximately 80 cm. Measurements were captured when perfect alignment, indicated by a green circle, was achieved.[23] Six readings were taken automatically, and the average values reported.

Statistical analysis
Data analysis was performed using the SPSS statistical package (V.28, IBM). ERG waveform characteristics, that is, amplitudes and implicit times of photopic a-wave, b-wave and 30-Hz response, were reported as mean, 95% CI and 5th–95th percentile range. Pearson's correlation test was used to evaluate the relationships between ERG waveform characteristics and age, SER, AL and K. Hierarchical regression analysis was used to evaluate the contribution of AL and the combination effect of AL and age on photopic a-wave, b-wave and 30-Hz flicker responses. Through this analysis, other than analysing the independent variables while controlling the former variable, it also evaluated the contribution of each variable. Statistical significance was defined as p<0.05.

RESULTS
Demographic and ocular biometric results
A total of 542 subjects aged 3–7 years (mean 5.0±0.9 years) from 11 kindergartens in Hong Kong participated in the study. Of these subjects, 63 with habitual VA worse than logMAR 0.3 due to poor attention and response, uncorrected refractive errors and the presence of amblyopia were excluded. Thus, 479 subjects (mean 5.0±0.9 years), of whom 218 were female (45.5%), were included in the data analysis. No statistically significant difference of any measurement was observed between males and females (all p>0.05). The overall mean SER was 0.80±1.00 D (range: −4.09 D to+4.93 D, n=473), the mean AL was 22.38±0.70 mm (range: 19.98 to 24.32 mm, n=466), and the mean K was 7.77±0.26 mm (range: 7.01 to 8.57 mm, n=433). Age was positively correlated with AL (r=0.36, p<0.001) and negatively correlated with SER (r=−0.12, p=0.01), but independent of mean K (r=−0.04, p=0.40). A complete set of photopic flash and flicker ERGs was successfully obtained from 428 subjects (89.4%). Thirty-five and 16 were only able to perform either flash protocol or flicker protocol, respectively. Demographical data were stratified with age and presented in table 1. There were three subjects with missing age data.

Photopic flash and 30-Hz flicker ERG responses
The waveform characteristics of photopic a-wave and b-wave responses, and 30-Hz flicker responses were expressed as amplitudes and implicit times. The mean values and 95% CI of all ERG parameters are presented in table 2. The 5th–95th percentile range of the ERG parameters is presented in the online supplemental material.

Relationships between ERG parameters and age
The b-wave amplitude (r=0.130; p<0.01) and 30-Hz flicker amplitude (r=0.120; p≤0.01) increased with age, while b-wave implicit time (r=−0.130; p<0.01) and 30-Hz flicker implicit time (r=−0.181; p≤0.001) decreased with age. No correlation was found between age and a-wave amplitude (p=0.06) and a-wave implicit time (p=0.50) of photopic flash response. Figure 1 shows the statistically significant relationships between ERG waveform characteristics and age. The remainder are shown in the online supplemental material. The mean values and 95% CI of amplitudes and implicit times of ERG response in different age groups are presented in table 1.

Relationships among ERG parameters, SER, AL and K
As shown in figure 2, AL was significantly negatively associated with a-wave amplitude (r=−0.131, p<0.01), 30-Hz flicker implicit time (r=−0.100, p=0.04), and positively

Table 1 Demographical data, mean and 95% CI of photopic a-wave and b-wave amplitudes and 30-Hz flicker amplitude in of all included subjects different age group

Demographical data			Amplitude (µV)			Implicit time (ms)		
Age (year) (total/female)	SER (D) Mean±SD	AL (mm) Mean±SD	A-wave Mean (95%CI)	B-wave Mean (95%CI)	30-Hz flicker Mean (95%CI)	A-wave Mean (95%CI)	B-wave Mean (95%CI)	30-Hz flicker Mean (95%CI)
3 (n=23/12)	0.84±1.02	21.67±0.60	−9.88 (−11.03 to −8.73)	34.65 (31.29 to 38.00)	34.87 (31.48 to 38.26)	11.61 (11.11 to 12.11)	28.79 (28.32 to 29.26)	25.36 (25.06 to 25.66)
4 (n=122/66)	0.95±1.07	22.10±0.69	−10.53 (−11.26 to −9.80)	36.56 (34.78 to 38.33)	38.08 (36.34 to 39.74)	11.79 (11.63 to 11.95)	28.28 (28.11 to 28.45)	24.87 (24.73 to 25.00)
5 (n=181/75)	0.73±0.91	22.44±0.66	−11.05 (−11.61 to −10.48)	37.75 (36.30 to 39.20)	39.27 (37.93 to 40.61)	11.80 (11.67 to 11.93)	28.07 (27.96 to 28.19)	24.73 (24.62 to 24.83)
6 (n=126/55)	0.77±0.91	22.58±0.65	−10.80 (−11.36 to −10.23)	39.17 (37.80 to 40.53)	39.27 (37.91 to 40.62)	11.57 (11.40 to 11.73)	28.14 (28.00 to 28.27)	24.72 (24.61 to 24.84)
7 (n=24/8)	0.44±1.37	22.89±0.57	−11.52 (−13.17 to −9.86)	38.03 (34.38 to 41.67)	39.74 (36.77 to 42.70)	11.86 (11.47 to 12.25)	28.34 (28.07 to 28.61)	24.79 (24.53 to 25.04)

AL, axial length; SER, spherical equivalent refraction.

associated with a-wave implicit time (r=0.116, p<0.01), b-wave amplitude (r=0.148, p<0.01), 30-Hz flicker amplitude (r=0.142, p<0.01), but not for b-wave implicit time (p=0.29). No statistically significant correlations were found between K and the ERG parameters except for 30-Hz flicker amplitude (r=0.13, p=0.01). No statistically significant correlation was found between SER and the ERG responses. Details are presented in the online supplemental material.

Multivariate analysis on effect of age and AL on ERG

Table 3 shows the statistical results of the hierarchical regressions. For b-wave amplitude, age contributed 1.5% (p=0.01) and AL contributed an additional 1.3% (p=0.02). For 30-Hz flicker amplitude, AL contributed 1.2% (p=0.02) and age contributed an additional 1.2% (p<0.01). For a-wave amplitude, the contribution of age was statistically insignificant (p=0.16), while the combination of age and AL contributed 1.7% (p=0.02). The contribution of age was also statistically insignificant for a-wave implicit time (p=0.57), but the combination of age and AL contributed 1.9% (p=0.02). In contrast, for b-wave implicit time, the contribution of age was 1.5% (p=0.01), while AL did not have additional contribution (p=0.89). For 30-Hz flicker implicit time, the contribution of age was 3.0% (p<0.001), but AL also did not have additional contribution (p=0.40).

DISCUSSION

ERG is a functional test for objectively examining retinal activities. However, it is relatively difficult and time-consuming to perform conventional ERG recordings on very young children, as mydriasis and a certain level of concentration from the subjects are needed. Thus, only limited ERG data sets of preschool children have been reported previously. In this study, use of RETeval allowed to establish a reference data set of photopic ffERG with a large sample of the preschool population. According to the RETeval user manual, a zero-phase 0.3-Hz high-pass filter reduces electrode drift and offset while preserving waveform timing, which is also suggested in ISCEV standard.[21] Carter et al compared the results from the standard ERG system and RETeval in a group of paediatric patients. They revealed a high level of agreement, while large limit of agreement was resulted in adult group, with smaller photopic a-wave and b-wave amplitude, higher flicker amplitude and shorter implicit times from RETeval.[24] Previous studies testing photopic flash ERG using RETeval also presented similar results as obtained in the present study.[20 25]

In this study, all participants were healthy subjects. Children with high refractive errors often coexist with retinal abnormalities. Paediatric patients with high refractive errors, including myopia, hyperopia and astigmatism, were having higher chance of diagnosing with retinal dysfunction than those with low refractive errors. The study by Logan et al reported that 25% of high myopes aged 3–10 years were having retinal dystrophies

Table 2 Mean and 95% CI of photopic a-wave and b-wave responses and 30-Hz flicker responses in current and previous studies

	Current study (n=479)	Asakawa et al (n=50)	Soekamto et al (n=20)	Nakamura et al (n=10)	Liu et al (n=25)
Age (year)	3–7	20–24	4–17	4–20	8–19
	Mean (95% CI)	Mean	Mean	Mean	Median
Amplitude (µV)					
A-wave	−10.83 (−11.07 to −10.47)	5.8	8.5	–	6
B-wave	37.76 (36.87 to 38.38)	21.1	38.8	–	27
30-Hz flicker	38.82 (37.74 to 39.19)	21.6	30.8	18.7	31
Implicit time (ms)					
A-wave	11.74 (11.68 to 11.83)	12.1	12.6	–	11
B-wave	28.18 (28.11 to 28.29)	28.2	28.1	–	28
30-Hz flicker	24.74 (24.74 to 24.87)	24.6	24.7	30.1	25

and amblyopia.[26] ffERG were also found decreased and delayed in patients with retinal dystrophy even when morphological examinations were unchanged.[27] Non-sedated handheld ERG device is a feasible tool for effective screening test of retinal dysfunction in paediatric patients with nystagmus.[16] Therefore, performing ERG in children with high refractive errors can aid clinical diagnosis and prevent confusing the real condition with others.[28]

Paediatric normative data

Previous studies have reported reference values of ERG using RETeval, but the sample sizes and age ranges varied considerably. Asakawa et al measured ERG from 100 eyes of 50 healthy young adult subjects aged 20–24 years in Japan[20] and Liu et al obtained ERG from 57

healthy subjects and 35 subjects with retinal diseases aged 8–65 years in Canada[25] using the ISCEV 5-step protocol, but the age ranges in these studies differ considerably from those in our study, which was 3–7 years. Soekamto et al also measured ERG using the same ISCEV protocol in 38 eyes of 20 healthy subjects aged 4–17 years in the USA, but the sample size was also too small.[17] Nakamura et al measured ERG with photopic 30-Hz flicker protocol from 50 healthy subjects and 35 diseased subjects aged 4–56 years in Japan with reduced cone responses due to hereditary and acquired retinal
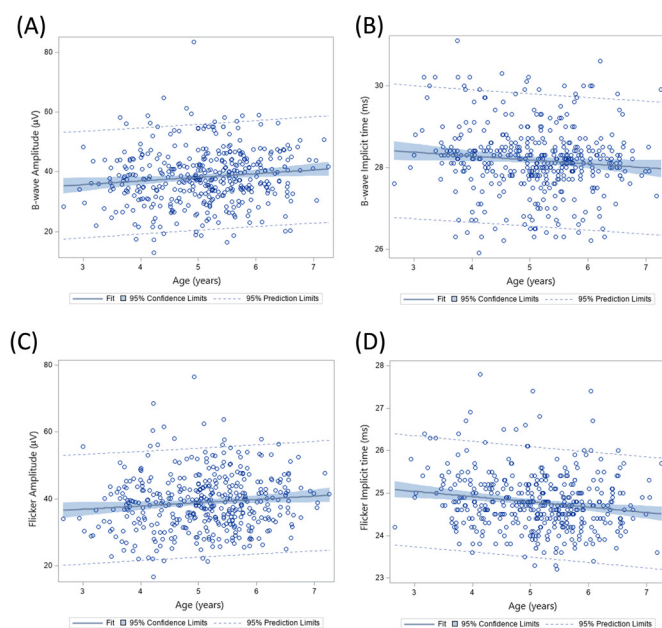
Figure 1 Pearson correlations between age and (A) b-wave amplitude, (B) b-wave implicit time, (C) 30-Hz flicker amplitude, (D) 30-Hz flicker implicit time.
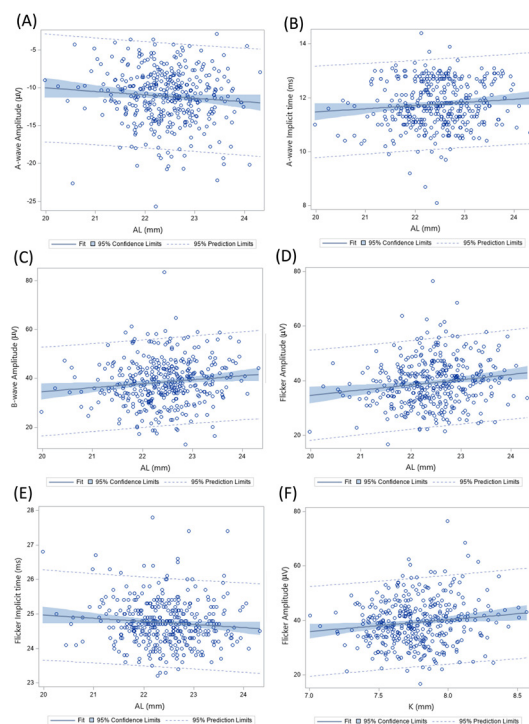
Figure 2 Pearson correlations between (A) a-wave amplitude, (B) a-wave implicit time, (C) b-wave amplitude, (D) 30-Hz flicker amplitude, (E) 30-Hz flicker implicit time and AL (F) 30-Hz flicker amplitude and K.

Table 3 Hierarchical regression analysis of axial length (AL) and combination of AL and age on photopic a-wave, b-wave and 30-Hz flicker responses

Models	Age			Age+AL			ΔR^2	P value
	R^2	F	P value	R^2	F	P value		
Amplitude (µV)								
A-wave	0.01	2.02	0.16	0.02	3.87	0.02*	0.01	0.02*
B-wave	0.02	6.76	0.01*	0.03	6.31	<0.01*	0.01	0.02*
30-Hz flicker	0.01	5.26	0.02*	0.02	5.28	<0.01*	0.01	0.02*
Implicit time (ms)								
A-wave	0.00	0.33	0.57	0.02	4.26	0.02*	0.02	<0.01*
B-wave	0.02	6.94	0.01*	0.02	3.48	0.03*	0.00	0.89
30-Hz flicker	0.03	12.95	<0.001*	0.03	6.83	0.001*	0.00	0.40

All variance inflation factors were below 1.2.
*Asterisk indicates statistical significance.

diseases.[19] All the above studies had limited sample sizes and may be unsuitable for use as a normative data set. The comparison of the studies is presented in table 2. Zhang et al measured ERG from 204 healthy subjects aged 0–18 years in China and the USA.[18] Their sample size was relatively large, but the age range was too broad and not limited to paediatrics, with only 68 children were at the same age group as the current study. They only performed 30-Hz flicker ERG while 2-Hz flash ERG was also conducted in the current study. Similar to the current study, they reported that flicker ERG responses had no statistically significant differences with gender. When comparing the current age-matched results from that obtained by their proposed regression line, the current study obtained a higher amplitude but similar implicit time. To the best of our knowledge, the current study had the largest sample size, and the targeted age range was focused, making it the most representative for the preschool population. This reference data set can be used to evaluate and grade the retinal function of paediatric patients with suspected retinal disease by using the portable ERG device in clinical practice. Yet this data set should be used with caution if it is incorporated into the device for non-mydriatic ERG recording as results might be affected. It is also a valuable set of data for later paediatric research studies related to retinal physiology.

Relationship between ERG, age and gender

The current study found that age was positively correlated with amplitudes and negatively correlated with implicit times of photopic b-wave and 30-Hz flicker. The effect of age on ERG response varies in previous studies. Fulton et al investigated rod, mixed rod-cone and cone ERG responses in normal infants, children and adults. They found increasing amplitude and decreasing implicit time with increasing age, which are coincident with the results obtained in the current study.[14] However, Birch and Anderson revealed decreasing log amplitudes of rod and cone responses and increasing b-wave implicit time with age in normal subjects aged 5–79 years.[15] The correlations between photopic responses obtained by RETeval and age were also investigated. Grace et al found no correlation with age for either 30-Hz flicker amplitude or implicit time in children aged 1–12 years.[16] Kato et al, using univariate linear regression analysis in subjects aged 20–29 years, reported that older age was weakly correlated with prolonged flicker implicit times,[29] which was in contrast to the paediatric population in this study. Soekamto et al noted a strong positive correlation between photopic a-wave implicit time and age in subjects aged 4–17 years.[17] Zhang et al further reported an exponential age dependence of the flicker amplitude and implicit time in subjects aged 0–18 years, in which age exponentially increased with amplitude, but decreased with implicit time before age of 11 years.[18] The current study also revealed similar trends in flicker amplitude and implicit time. Compared with the previous studies, the current results from a large sample of more than 400 preschool children with a focused age range suggested that there would be ongoing retinal maturation during preschool years, in terms of increasing amplitude and early shifting of peak time.

The current study also found no statistically significant difference of any measurement between males and females, which was coincident with previous studies. The study by Zhang et al with similar sample size found no statistical difference between measurements in gender.[18] Chia et al performing full-field ERG in Singapore children also found no statistical difference in gender.[13] Parvaresh et al investigating normal values of ffERG in Iranian population aged 1–80 years also reported no statistical differences between genders in all age groups.[30]

Relationship between ERG, SER and AL

A longer AL was shown to be significantly associated with lower a-wave amplitude, but greater b-wave and 30-Hz flicker amplitudes, as well as a prolonged a-wave implicit time and shortened 30-Hz flicker implicit time. In a previous report, Westall *et al* found significant differences in rod, cone and 30-Hz flicker ERG amplitudes among high myopia, mild myopia and low refractive error groups aged 13–37 years. Significant reduction in the ERG amplitudes was associated with increasing AL ranging from 22.2 to 30.0 mm.[31] Sachidanandam *et al* showed amplitude reduction and implicit time delay in ERG responses with increasing AL in young adults with AL ranging from 21.79 to 30.55 mm.[32] Chia *et al* reported a slightly decreasing but statistically insignificant tendency of photopic b-wave amplitude with increasing AL in myopic children, and that refractive error was independent of scotopic, photopic and 30-Hz flicker amplitudes and implicit times.[13] The above-mentioned studies found reducing amplitude with increasing AL, and the same correlation was obtained only for a-wave but not for b-wave and 30-Hz responses in the current study. Using multivariate linear regression analysis, Kato *et al* demonstrated AL as an independent factor affecting the implicit time of 30-Hz flicker ERG in young adults, with 1 mm increase in AL associated with 0.39 ms delay in implicit time.[29] In contrast, such an association was not found in the current study. A more recent study by Wan *et al* showed significant positive correlations between amplitudes of a-wave and b-wave in dark-adapted scotopic ERG and refractive power among young emmetropes, low, moderate and high myopes, but cone function measured by photopic ERG was independent of refractive error.[33] The inconsistent results from different studies may be due to the different ranges of age and AL of subjects.

Owing to normal development, age would be positively correlated with AL, but despite this, collinearity was tolerable in the multivariate analysis. From the current findings, the combination effect of AL and age was shown to have significant association with the photopic a-wave, b-wave and 30-Hz flicker responses. For b-wave amplitude, age was found to have a greater contribution than AL, while 30-Hz flicker amplitude had about equal contribution from age and AL. The results indicated that both age and AL, implying refractive status of the children, had independent contributions to ERG results.

In a 1-year longitudinal study, school-aged myopia progression was reported to be associated with a reduced foveal ERG response as measured by a modified paradigm of multifocal ERG.[34] Consistently in two other longitudinal studies, emmetropic children with subclinical decrease of photopic inner retinal function in the central retina were found to be more likely to develop myopia[35] and to have longer axial elongation.[36] It speculates that the central retinal response, which may be represented by photopic ERG response, could be related to myopia progression in young children.

Limitations

Eye movement during the ERG recording is one of the limitations of this study. The eye movements were monitored by the examiner using the built-in pupil tracking camera, but the fixation stability varied among subjects, as some were very young and had less patience to cooperate throughout the whole measurement. The eye movements with non-dilated pupils may cause artefacts that lower the reliability of results, which was alleviated by the autoreject function on artefact waveforms. In addition, Kato *et al* showed that pupil size would affect the flicker ERG responses recorded with RETeval, which was not controlled in the current study, although stimulus intensity was real time adjusted by pupillography with the non-mydriatic protocol.[37] In addition, the placement of standard sensor strip electrode was not fitted for some preschool children, and the position of electrodes may affect the recorded response.[38]

In conclusion, a normative reference data set of photopic ffERG in Hong Kong preschool children was established, which can be used as a reference for future clinical studies and applications. Photopic ERG was found to be correlated with age and AL, which suggested an ongoing retinal maturation in preschool children. Implication of the retinal role in refractive error development warrants further investigation.

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