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Development of ERG responses: The ISCEV rod, maximal and cone responses in normal subjects

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Abstract

Purpose: Summarize ISCEV ERG responses from normal infants and children. *Methods:* The amplitudes and implicit times of the ISCEV rod, maximal dark-adapted and cone responses from a total of 409 normal infants (n = 128), children and adult controls were compiled. The subjects, aged 1 week to 52 years, were divided into seven age groups, including four in infancy (< 52 weeks). The response parameters for each age group were summarized as percentiles. *Results:* In each ISCEV condition, the youngest infants (1–5 weeks) had significantly smaller amplitudes and longer implicit times than adults. Amplitude increased and implicit time decreased systematically with age. *Conclusions:* The developmental changes in ERG responses are significant. The medians and ranges herein provide provisional norms against which the ERG responses from pediatric patients can be compared.

Introduction

Electroretinographic (ERG) testing may be needed to secure a diagnosis in infants and children with visual impairment. It is known that infants have significant immaturities of retinal processes [1–7] and the ERG responses in young infants are smaller than those in adults [6, 8–12]. However, the normal ranges of amplitudes and implicit times through infancy and childhood remain incompletely defined in conditions commonly used for clinical testing.

With the aim of providing provisional ranges of normal against which the ERG responses of pediatric patients may be compared, two laboratories with longstanding interest in ERG testing of infants and children have summarized ISCEV ERG responses [13] from more than 400 normal subjects, three quarters of whom are within the pediatric age range. Included in this report are the ISCEV responses developed by the rods (in the dark adapted eye), the maximal response of the dark-adapted eye and the response developed by the cones (in the light adapted eye). The development of the normal response to rapidly repeated stimuli (flicker) has been little studied using contemporary procedures, and the complexities of the development of the oscillatory potentials remain under investigation. Therefore, the development of the oscillatory potentials and flicker responses are not considered herein.

Methods

Electroretinography

Both laboratories, one in Toronto, the other in Boston, used similar procedures for collecting the primary data. The pupil was dilated and the subject was dark-adapted for 30 min. After dark adaptation, in dim red light, proparacaine, 0.5%, was instilled and a Burian Allen bipolar electrode was placed on the cornea. The ground electrode was placed over the mastoid (Boston) or forehead (Toronto). A strobe delivered brief stimuli via an integrating sphere. All responses were differentially amplified, displayed on an oscilloscope, digitized and stored on disc (Table 1). An adjustable voltage window was used to reject records contaminated by artifacts. Up to 16 responses were averaged in each stimulus condition. The interstimulus interval ranged from 2 to 60 s and was selected so that subsequent b-wave amplitudes were not attenuated. Many, but not all, of the responses presented herein have been embedded in research reports on the development of

Table 1. Recording and stimulus characteristics

	Boston	Toronto
Data acquisition		
Gain	1000	2833
Bandpass	1–1000 Hz	0.3–300 Hz
Digitization rate	2.5 KHz	1 KHz
Stimuli		
Strobe	Novatron (Dallas, TX)	Grass PS 22
Color temperature	5200 K	6677 K
Standard flash	*2.25 cds/m^2	2 cds/m^2
	(2.45 log scot td s)**	2.40 log scot td s)**
Rod	Blue (Wratten 47B; $\lambda < 510$ nm)	White
Maximal	Blue (Wratten 47B)	White
Cone	Red (Wratten 29; $\lambda > 610$ nm)	White

*Blue.
**Assuming 8 mm pupil.

retinal processes done in the Boston [1–5, 7] and in a study of ERG development [6].

From the responses to a several log unit range of stimuli used for primary data collection [1, 4–7], those selected for this report were evoked by the stimuli listed in Table 1. While within the ISCEV specifications and with standard flash nearly equal in Boston and Toronto, there were differences between the two laboratories. The stimuli used in Boston were blue flashes for ISCEV rod and maximal responses, and red flashes for the ISCEV cone response. In Toronto, all stimuli were white.

Subjects

The data are from 409 subjects. The distribution of ages at ERG test indicates that 305 (75%) were under 20 years, and of these 128 (31%) were infants < 52 weeks (Figure 1). All infants and children were born at term (40 ± 2 weeks gestation). The infants were divided into four age groups of 25–43 infants (Figure 1; Table 2). The sources of subjects are also shown in Table 2. Young children are seldom recruited for normal ERG studies using corneal contact electrodes. The majority of the 15–52 weeks and 1–10-year-olds (Table 2) had been referred for clinical testing. The Boston data are from 147 healthy subjects with normal eyes, aged 2 weeks to 52 years, who were recruited specifically for ERG research studies. Data from 93 have been reported in the research studies [1–5, 7]. An additional 24 had been referred for clinical ERG testing but were found to have perfectly normal eyes; each has remained normal for 3–8 years after the ERG test. All Boston subjects were tested without anesthesia or sedation. The Toronto data are from 43 normal, healthy subjects recruited for study, and from 195 patients who were referred for ERG testing, but were found to have normal eyes. For Toronto adults, no significant difference on any parameter was found between referred versus recruited (Table 2). Among the Toronto patients, 47 had idiopathic, congenital nystagmus, and 29 were tested under sedation with chloral hydrate [6]. Within an age group, no significant difference on any parameter was found between sedated versus not sedated, or nystagmus versus no nystagmus. Therefore, the responses of the patients with nystagmus and those tested under sedation are included. In the research studies only one eye was tested. For patients, data from only one eye, selected arbitrarily, were included.

Analyses

The responses of the Toronto and Boston adults were compared in each ISCEV condition (Table 3). The largest Boston–Toronto difference is in the cone a-wave amplitude. Possibly the stimulus conditions (red flashes in Boston, white flashes in Toronto) contribute to the difference in the a-wave amplitudes. However, because the other parameters of the cone response (a-wave implicit time; b-wave amplitude; b-wave implicit time) do not differ between Boston and Toronto, no clear biological or experimental explanation for the disparity in cone a-wave amplitudes emerges. For the three other parameters with statistically significant

Table 2. Number and source of subjects

Group	Age	Location				Total
		Boston		Toronto		
		Referred	Recruited	Referred	Recruited	
1	1–5 weeks	0	28	0	3	31
2	5–10 weeks	0	23	1	1	25
3	10–15 weeks	0	41	2	0	43
4	15–52 weeks	3	0	25	1	29
5	1–10 years	18	3	84	0	105
6	10–20 years	3	16	52	1	72
7	⩾20 years	0	36	31	37	104
Total		24	147	195	43	409

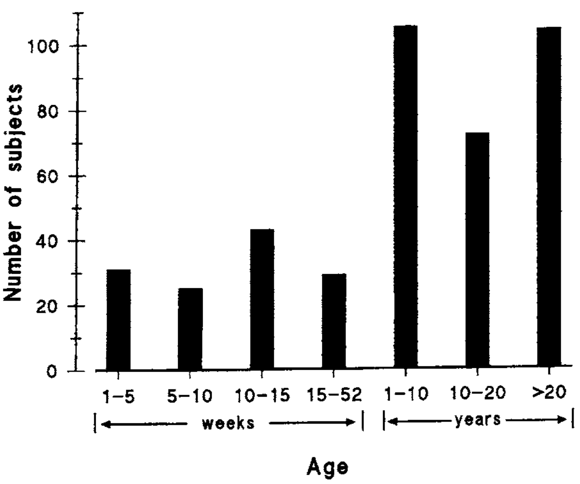

Figure 1. The number of subjects in each of the four age groups of infants and in the three older age groups are plotted.

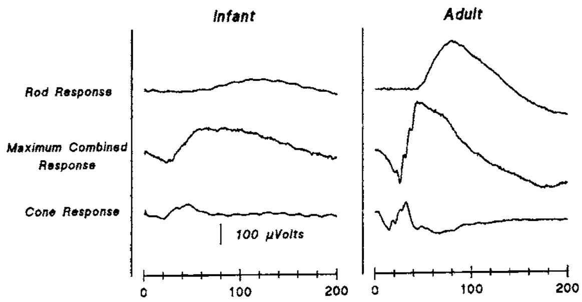

Figure 2. Sample records of the ISCEV rod, maximal and cone response are shown for a 4-week-old infant and an adult subject.

differences between Boston and Toronto (rod b-wave implicit time; maximal a-wave amplitude; maximal b-wave amplitude), all Toronto results are entirely within the observed Boston range. Therefore, the data from the two laboratories were combined for further analysis. Within an age group, the median and range summarized each parameter.

Results

Sample records of a 4-week-old infant and an adult (Figure 2) show amplitudes are smaller and implicit times longer in the infant. In all test conditions the median amplitudes and implicit times differ significantly between the 1–5-week-old infants and adults (Table 4). Of note, eight (26%) of the 31 infants in the youngest group had no detectable ISCEV rod response.

From age 5 weeks onward, all infants had detectable responses in all of the ISCEV conditions. The ranges of the infants' and adults' response parameters do not differ significantly.

The median b-wave amplitudes for the ISCEV rod, maximal and cone responses increase systematically until adulthood (Figures 3–5). In all ISCEV conditions, the ranges in infants never exceeded the ranges in adults (Figures 3–5). The median b-wave amplitudes in the youngest group are 15% (rod), 32% (maximal) and 46% (cone) of the medians for adults. It is known that primate cones mature earlier than rods [14]. The numeric values of the medians and ranges of the b-wave amplitudes, and also a-wave amplitudes and a- and b-wave implicit times are summarized in Tables 5–7. The implicit times of the b-waves decrease systematically with age for the ISCEV maximal and cone responses, but for the rod response vary little with age.

Table 3. ISCEV responses in Boston and Toronto adults

			Median (range)		
			Boston ($n = 36$)	Toronto ($n = 68$)	Mann–Whitney U (p value)
Rod	B-wave	Amplitude	253 (98–428)	231 (101–367)	936 ($p = 0.118$)
		Implicit time	79 (59–129)	114 (94–127)	319 ($p < 0.01$)
Maximal	A-wave	Amplitude	184 (58–448)	274 (133–434)	601 ($p < 0.01$)
		Implicit time	18 (16–30)	20 (17–22)	1020 ($p = 0.381$)
	B-wave	Amplitude	425 (150–889)	543 (391–829)	524 ($p < 0.01$)
		Implicit time	46 (34–58)	45 (34–53)	961 ($p = 0.199$)
Cone	A-wave	Amplitude	92 (69–103)	42 (23–106)	8 ($p < 0.01$)
		Implicit time	15 (14–16)	14 (12–20)	142 ($p = 0.091$)
	B-wave	Amplitude	137 (103–161)	164 (76–285)	148 ($p = 0.143$)
		Implicit time	28 (25–32)	29 (25–31)	197 ($p = 0.596$)
Age (years)			22 (20–52)	30 (20–40)	692 ($p < 0.01$)

Table 4. Comparison of ISCEV responses in infants (1–5 weeks) and adults (⩾ 20 years)

			Median (range)		
			Infants ($n = 31$)	Adults ($n = 104$)	Mann–Whitney U (p value)
Rod	B-wave	Amplitude*	42 (11–206)	244 (98–429)	11.5 ($p < 0.01$)
		Implicit time*	105 (88–133)	110 (52–129)	156 ($p < 0.01$)
Maximal	A-wave	Amplitude	39 (9–125)	266 (63–448)	17.5 ($p < 0.01$)
		Implicit time	23 (16–38)	20 (15–30)	316 ($p = 0.053$)
	B-wave	Amplitude	137 (25–370)	517 (150–889)	31 ($p < 0.01$)
		Implicit time	65 (51–105)	45 (34–58)	11.5 ($p < 0.01$)
Cone	A-wave	Amplitude	30 (15–60)	42 (23–106)	0 ($p < 0.01$)
		Implicit time	19 (15–21)	14 (12–20)	6.5 ($p < 0.01$)
	B-wave	Amplitude	60 (10–103)	160 (76–285)	1.5 ($p < 0.01$)
		Implicit time	36 (31–41)	28 (25–32)	2 ($p < 0.01$)

*The median and range for the 23 infants with detectable ISCEV rod response are shown.

Table 5. Percentiles for ISCEV rod response

Age group	Amplitude (μV)					Implicit time (ms)				
	5	25	50	75	95	5	25	50	75	95
B-wave										
1–5 weeks	12	23	42	61	146	92	95	105	114	131
5–10 weeks	23	37	63	114	141	71	94	104	109	123
10–15 weeks	46	65	80	98	146	74	92	98	105	113
15–52 weeks	60	98	129	143	191	99	114	119	124	129
1–10 years	82	120	161	224	331	83	108	116	121	126
10–20 years	130	193	235	293	377	67	98	110	116	124
⩾20 years	149	195	244	285	360	65	98	110	118	125

Table 6. Percentiles for ISCEV maximal response

Age group	Amplitude (μV)					Implicit time (ms)				
	5	25	50	75	95	5	25	50	75	95
A-wave										
1–5 weeks	10	19	39	57	82	19	21	23	26	30
5–10 weeks	24	43	63	80	103	20	20	21	23	25
10–15 weeks	14	29	75	114	143	19	20	22	24	29
15–52 weeks	93	123	145	154	203	17	21	21	22	24
1–10 years	103	144	190	231	322	16	20	21	22	25
10–20 years	104	199	264	309	368	16	19	20	22	26
⩾ 20 years	115	212	266	305	363	16	19	20	21	27
B-wave										
1–5 weeks	42	81	137	195	316	54	60	65	75	95
5–10 weeks	140	184	253	310	385	51	56	61	63	72
10–15 weeks	114	159	271	356	423	51	53	55	66	75
15–52 weeks	353	420	452	507	593	45	49	53	55	58
1–10 years	339	421	473	553	660	42	45	47	50	55
10–20 years	366	465	538	630	722	40	44	46	48	52
⩾ 20 years	322	461	517	609	711	36	43	45	48	53

Table 7. Percentiles for ISCEV cone response

Age group	Amplitude (μV)					Implicit time (ms)				
	5	25	50	75	95	5	25	50	75	95
A-wave										
1–5 weeks	16	24	30	40	61	15	18	19	20	21
5–10 weeks	22	30	43	46	69	14	16	18	19	20
10–15 weeks	18	30	43	46	52	15	15	16	18	19
15–52 weeks	14	23	27	39	68	13	15	15	17	18
1–10 years	16	26	34	50	62	13	14	15	16	17
10–20 years	17	36	43	60	101	13	14	14	15	16
⩾ 20 years	27	35	42	56	92	13	14	14	15	16
B-wave										
1–5 weeks	33	43	60	84	103	33	35	36	40	40
5–10 weeks	78	93	102	115	140	30	33	36	38	39
10–15 weeks	37	71	92	123	141	30	31	35	37	38
15–52 weeks	92	112	128	152	181	27	29	30	31	33
1–10 years	67	102	128	151	211	25	27	29	30	32
10–20 years	95	134	155	195	259	26	27	28	29	32
⩾ 20 years	88	117	160	188	235	25	27	28	29	31

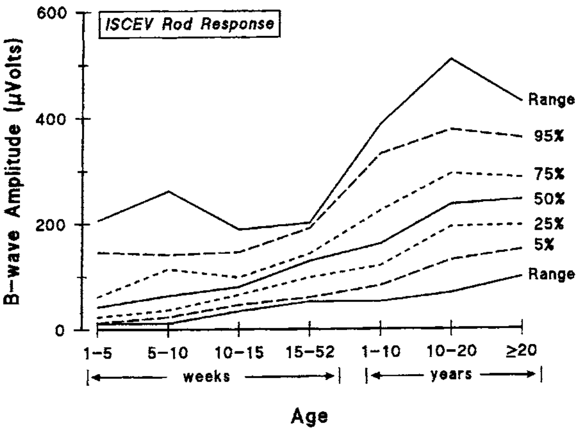

Figure 3. The 5th, 25th, 50th (median), 75th, 95th percentiles and full range of observed b-wave amplitudes of the ISCEV rod response are plotted as a function of age. The values for each age group are connected by line segments. The numeric values of the percentiles are included in Table 5.

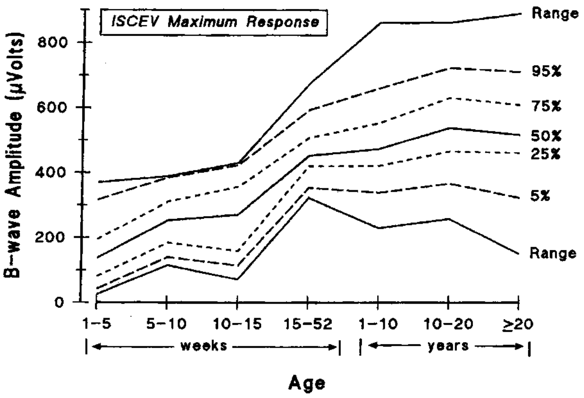

Figure 4. The 5th, 25th, 50th (median), 75th and 95th percentiles and full range of b-wave amplitudes of the ISCEV maximal response are plotted as a function of age. The values for each age group are connected by line segments. The numeric values of the percentiles are included in Table 6.

The median b-wave amplitude for the ISCEV rod response is near the lower end of the observed range for infants less than 15 weeks old (Figure 3). With the exception of the ISCEV rod response under age 15 weeks, the distribution of the amplitudes within an age group does not differ significantly from a normal distribution in any ISCEV condition. For these groups, variability is never significantly greater in infants and children than in adults. For the normally distributed data, a parametric statistic, the prediction interval [15], may be used to calculate expected limits of normal values. The lower limits of the 95% prediction interval so derived are non-detectable, zero or less, until

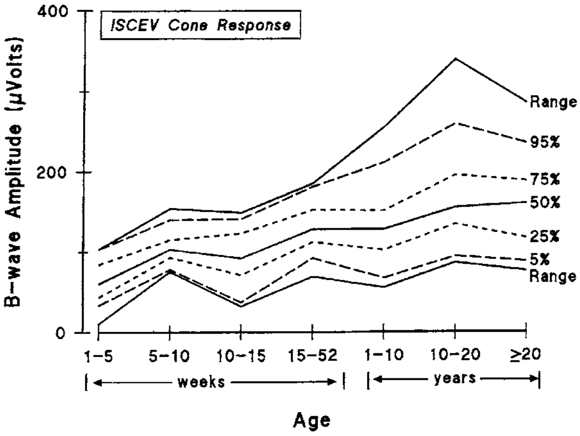

Figure 5. The 5th, 25th, 50th, 75th and 95th percentiles and full range of b-wave amplitudes of the ISCEV cone response are plotted as a function of age. The values for each age group are connected by line segments. The numeric values of the percentiles are included in Table 7.

after age 15 weeks even for the ISCEV maximal and cone b-wave amplitudes. The prediction intervals for the ISCEV responses are at www.infantvision.org.

Discussion

The ERG responses of normal pediatric subjects (Tables 5–7) provide provisional norms against which the ERG responses of pediatric patients may be compared. To our knowledge, we have presented the largest sample of term born infants and children for whom such data are available. A third of the 409 subjects are infants and three-quarters are under 20 years of age. We note that at post-term ages, healthy infants with a history of preterm birth (12) have b-wave amplitudes within the range of the term born infants (Figures 3–5).

It appears that considerable caution is in order when interpreting the ISCEV responses of infants because of small amplitudes, not greater variability. In the youngest group, age 1–5 weeks, a quarter of these normal infants had no detectable ISCEV rod response. Furthermore, it is sobering to acknowledge that the calculated lower limits of normal b-wave amplitudes for all three ISCEV conditions include non-detectable responses until late infancy.

What are practical strategies for dealing with the realities of small response amplitudes in infancy? One that serves us well is to test with a larger range of stimuli. With this approach, every infant, even the youngest, has responses sufficient for thorough characterization of scotopic b-waves [1]. To test the dark adapted eye, we use at least a three log unit range of stimuli starting with dim flashes that produce a just detectable b-wave and continue through those that saturate the amplitude of the b-wave (e.g., Ref. [1]). One obtains a set of responses, the majority of which are well above the noise level from early infancy onward [1]. For amplitudes well above the noise level, little signal averaging is required to obtain clear records. Small amplitudes, such as obtained from young infants in the ISCEV rod condition, may require a great deal of averaging to demonstrate the signal in the midst of noise due to blinks, eye movements and other artifacts. With similar, or less, time and effort, the stimulus/response function yields information that may be related to the biological properties of retinal cells [1]. Furthermore, the parameters of the stimulus/response functions typically have lower variability with the standard deviations about 15% of the normal mean [16]. Standard deviations for the amplitudes of a- and b-wave responses to a particular stimulus are typically greater. For the adults included in this report, the standard deviations of the b-wave amplitudes (rod, maximal, and cone) are about 25% of the mean.

Another practical option worth considering is to repeat testing of the infant a few weeks or months later. Particularly if the initial impression is that the infant's ISCEV responses are abnormal, re-test data can help confirm, or refute, the original impression. The normal developmental increase in ERG response amplitudes tends to support reliable assessment of the infant's retinal function on repeat testing.

Finally, we are reminded that ERG responses are not studied in isolation, but in the context of the child's history, results of ophthalmic examination and other clinical data. The ERG results are but one piece of the diagnostic puzzle.

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