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Retina

Electroretinography With the RM Electrode: Normative Reference Ranges, Variation With Age, and Comparison With the Burian–Allen Electrode

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Purpose: The RM Electrode is a new, single-use, soft-contact lens electrode for recording the full-field electroretinogram (ffERG). Aims were (1) to define the ffERG reference ranges for the RM Electrode, with age, from healthy volunteers and (2) to compare ffERGs recorded with the RM Electrode and Burian–Allen (BA) electrode.

Methods: The ffERGs were recorded using the International Society of Clinical Electrophysiology of Vision (ISCEV) standard, including four ISCEV extended protocols: dark-adapted red flash, photopic negative response, ON–OFF, and S-cones. Electroretinogram (ERG) parameters and recording stability, measured from the percent coefficient of variation (%CV), were compared across electrodes.

Results: Participants were 40 (19 female) healthy volunteers aged 39.4 ± 15.7 years. Participants' race (white/black/Asian = 58%/20%/18%) and ethnicity (Hispanic = 10%) were congruent with the US 2020 Census. All amplitudes and implicit times followed a log-normal distribution (except photopic b-wave and ON–OFF amplitudes); most parameters varied with age. RM Electrode dark-adapted a-wave and light-adapted b-wave amplitudes were 18% ($P = 0.02$) and 20% ($P < 0.001$) larger than the BA electrode; scotopic b-wave amplitudes did not differ. The 30-Hz ERGs were more stable for the RM Electrode (median [interquartile range] %CV = 12.3% [7.6–17.6]) compared with the BA electrode (%CV = 16.7% [12.5–26.8] ($P = 0.001$).

Conclusions: RM Electrode parameters and interflash ERG stability were comparable to or better than those for the BA electrode.

Translational Relevance: The derived reference ranges for the RM Electrode allow easy adoption of this disposable contact lens electrode that mitigates possible cross-contamination between patients.

Introduction

The full-field electroretinogram (ffERG) is a measure of the change of voltage across the retina in response to a brief flash of light.[1] Several electrodes are commercially available for recording the ffERG. Contact lens electrodes (CLEs) such as the Burian–Allen (BA) and Jet are placed directly on the cornea after application of a topical anesthetic. Other forms of electrodes that have a lower area of contact with the cornea either hook over the lower eyelid (e.g., gold foil) or lie along the rim of the lower eyelid (e.g., Dawson, Trick, Litzkow [DTL]); topical anesthetic may or may not be required. Skin electrodes placed centrally on the lower eyelid may also be used to record the electroretinogram (ERG).[2]

CLEs have considerably larger amplitudes, better signal-to-noise ratios, and more stable recordings than other electrodes used to record the ERG.[3–6] However, skin electrodes and those placed within or along the lower eyelid are generally better tolerated by patients.[7,8]

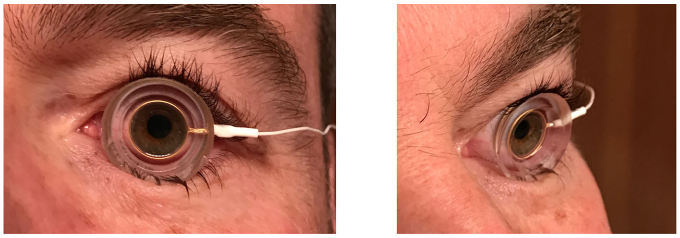

Figure 1. Front and side views of the RM Electrode in the eye. Photographs provided by RetMap (Chicago, IL, USA).

The discomfort associated with current CLEs could be attributed to several factors, including (1) the use of a hard contact lens, (2) the raised posts on the Jet electrode that may cause pain during eyelid closure, or (3) the presence and associated pressure of a large speculum used to hold the BA electrode in the eye.

The BA electrode is reusable, which raises issues regarding sterilization, particularly with respect to the presence of prions, which may be found in the tear fluid of patients with Creutzfeldt–Jakob disease.[9]

Recently, a new CLE cleared by the US Food and Drug Administration (FDA), the RM Electrode (RetMap, Chicago, IL, USA) became commercially available (Fig. 1). The RM Electrode is single-use, which mitigates infection risk and avoids issues associated with sterilization. An important first step in adopting any new ERG electrode into a clinic is to describe the normative reference range.

Normative reference ranges, as a function of age, exist for the ffERG recorded with both CLEs[10,11] and non-CLEs.[12–16] However, much of these data were collected either before the publication of the first International Society of Clinical Electrophysiology of Vision (ISCEV) ffERG standard in 1989 (renewed most recently in 2022) and/or before the publication of the ISCEV extended ERG protocols between 2018 and 2020. For many of the reported reference ERG data sets, there is little information beyond age and/or sex about the healthy volunteers recruited. Some normative data sets were not necessarily from representative populations. For example, several studies recruited volunteers from staff, friends, or students,[17–20] while others limited analysis to white, Hispanic, and Asian subjects[11] or only published data from Caucasians.[10,16]

The first aim of the current study was to describe the reference ranges for ERG parameters recorded with the RM Electrode in accordance with the ISCEV ffERG protocol,[1] including the following extended ERG protocols (dark-adapted red, ON–OFF, S-cone, photopic negative response [PhNR]).[21–24] We sought to recruit from healthy volunteers representative of the US population across a wide age range. The second aim was to compare the stability and ERG parameter values of the RM Electrode with our current gold standard, the BA contact lens electrode.

Methods

Forty healthy volunteers aged 20 to 74 years were recruited from the Clinical Research Volunteer Program at the National Institutes of Health (NIH) Clinical Center or responded to the posting of this trial on ClinicalTrials.gov (identifier: NCT02617966). All participants had visual acuity of 20/20 or better and were deemed visually healthy by a full ophthalmic examination. The study was approved by the Institutional Review Board of the NIH. All participants provided informed consent after explanation of the nature and possible consequences of the study. Sex, race, and ethnicity were self-reported by participants.

Overview of the RM Electrode

The RM Electrode, shown in Figure 1, was developed by John Hetling and colleagues at RetMap (first described in Rahmani S. *IOVS*. 2017;58:ARVO E-Abstract 4890).

The RM Electrode has subsequently undergone development and is currently marketed through RetMap. A detailed description of the RM Electrode, including features, comfort, safety, and use, are given in the Appendix.

Experiment 1: Comparison of the RM Electrode With the BA Electrode

Experiment 1 ERG recordings were made on a Sunburst Ganzfeld UTAS electrophysiology system (LKC, Gaithersburg, MD, USA). Stimulus and recording conditions for experiment 1 are given in Supplementary Table S1. A total of 23 participants were recorded for experiment 1. Participants were dilated and placed in the dark for 30 minutes before the start of ERG recording. An RM Electrode was placed in one eye, and a bipolar BA electrode (Hansen Ophthalmic Development Laboratory, Bellingham WA, USA) was placed in the contralateral eye under dim red light illumination. Skin electrodes, placed on the forehead and ipsilateral outer canthus of the eye with the RM Electrode, served as ground and reference, respectively. A third skin electrode, placed on the ipsilateral outer canthus of the eye with the BA electrode, served as the reference for a subset of monopolar recordings (see Results). Scotopic and photopic ffERGs were then recorded according to the ISCEV standards.[1]

Experiment 2: Reference Ranges for the RM Electrode

Experiment 2 ERG recordings were made on a MonCvONE CR++ (MetroVision, Pérenchies, France). Stimulus and recording conditions for all experiment 2 protocols are given in Supplementary Tables S2 and S3. Participants from experiment 1 agreed to a second set of recordings; 17 additional participants also completed these recordings (N = 40 total). Participants were placed in the dark for 30 minutes before the start of ERG recording. An RM Electrode (RetMap) was placed in one eye under dim red illumination. Skin electrodes, placed on the forehead and ipsilateral outer canthus, served as ground and reference, respectively. Scotopic ffERGs were first recorded to a dim red flash, according to the ISCEV extended protocol for the dark-adapted red flash ERG.[21] ISCEV standard ffERGs were then recorded.[1] Subsequently, ffERGs were recorded according to the ISCEV extended protocols for the photopic ON–OFF,[22] S-cone,[23] and PhNR.[24] PhNRs were recorded for white-on-white (LA3), red-on-blue ($PhNR_{R/B}$), and blue-on-yellow ($PhNR_{B/Y}$) stimuli. PhNR amplitude was measured (1) from the baseline to the minimum point in the trough following the b-wave (LA3 BT, $PhNR_{R/B}$ BT, $PhNR_{B/Y}$ BT) and (2) from the peak of the b-wave to the same trough minimum (LA3 PT, $PhNR_{R/B}$ PT, $PhNR_{B/Y}$ PT).

Statistics

Comparison of the RM Electrode With the BA Electrode

Comparison of ERG Parameters. To compare ERG amplitudes and implicit times between RM Electrode and BA electrodes, multiple t-tests were done for ERG parameters grouped by common components (e.g., scotopic b-wave amplitudes for DA01, DA3, and DA30). The Holm–Šídák method was used to correct for multiple comparisons.

Comparison of ERG Recording Stability. To compare the stability of the ERG responses from each electrode, we measured the variability of a- and/or b-wave amplitudes from the individual responses that were averaged for each ERG response. For example, variation of the b-wave amplitude was calculated from the eight flash responses for the LA3 average. Similarly, variations in the a- and b-wave amplitudes were calculated from the three flash responses for the DA30 average (Supplementary Fig. S1). Variability was compared between the electrodes from the calculation of the coefficient of variation (CV), defined as the ratio of the standard deviation to the mean ($CV = \sigma/\mu$), expressed as a percentage (%CV). CV does not depend on absolute values and, therefore, provides a means of comparing ERG variability between the two electrodes across a wide range of amplitudes.

Testing Parameter Distributions for Normality

We used a three-step approach to test the null hypothesis that each ERG parameter was sampled from a population that follows a Gaussian (normal) distribution. First, we used the D'Agostino and Pearson and Anderson–Darling tests to compare normal and log-normal distributions (Prism; GraphPad Software, La Jolla, CA, USA). Prism uses a likelihood test and computes the relative likelihood, expressed as a percentage, that data were sampled from a normal or log-normal distribution. Second, we examined quantile–quantile plots of the predicted values against actual values: points would be fit by a straight line if the data were sampled from a Gaussian distribution. Third, we visually inspected distributions to assess whether they were consistent with normal, log-normal, or another distribution. We accepted the null hypothesis (Gaussian distribution) unless the combined approach indicated a log-normal (or other) distribution.

Calculation of Reference Range

In almost all clinical cases, ERGs are assessed in terms of whether a patient's amplitudes are reduced and/or implicit times are delayed. Therefore, we used a single-sided estimate (fifth percentile) of a parameter's distribution to define the lower limit of the normal reference range for amplitude (mean −1.65 standard deviation [SD]) and upper limit of the normal reference interval for implicit time (mean + 1.65 SD).

Calculating Precision of Reference Limits

Given the relatively small number of healthy volunteers, we also calculated the precision of each reference limit, expressed as the 90% confidence interval (CI), calculated as[25]

$$90\%\,\mathrm{CI} = \text{lower limit/upper limit} \pm 2.81\left(\mathrm{SD}/\sqrt{\mathrm{N}}\right) \quad (1)$$

where SD is the standard deviation of the sample and N is the number of data points.

Comparison of the PhNR Amplitudes

A mixed-effects model with stimulus type (white-on-white, red-on-blue, blue-on-yellow) as the main factor and patients as random factors was used to compare PhNR parameters.

Results

Participant Demographics

Participants were 40 healthy volunteers aged 20 to 74 years (mean ± SD = 39.4 ± 15.7 years), of whom 19 were female (47%). Participants self-identified race as white (*n* = 23; 58%), black (*n* = 8; 20%), or Asian (*n* = 7; 18%); two participants chose not to self-identify with a race. Participants self-identified ethnicity as Hispanic or Latino (*n* = 4; 10%) or not Hispanic or Latino (*n* = 36; 90%). The number of patients per decade was well stratified for the third to seventh decades of life, although there was an overrepresentation of participants between 20 and 29 years of age (Supplementary Table S4).

Figure 2 shows representative examples of all ffERG recordings, along with parameter measurements, made from a 24-year-old healthy volunteer. ffERGs from a 74-year-old participant, the oldest in our study, were smaller but had the same morphology (Supplementary Fig. S2).

ERG Parameter Distributions

Scotopic ERG amplitudes and scotopic b/a and x/b ratios were all best described by log-normal distributions (Supplementary Table S5). Photopic S-cone and PhNR BT amplitudes and PhNR BT/b-wave ratios were also best described by log-normal distributions

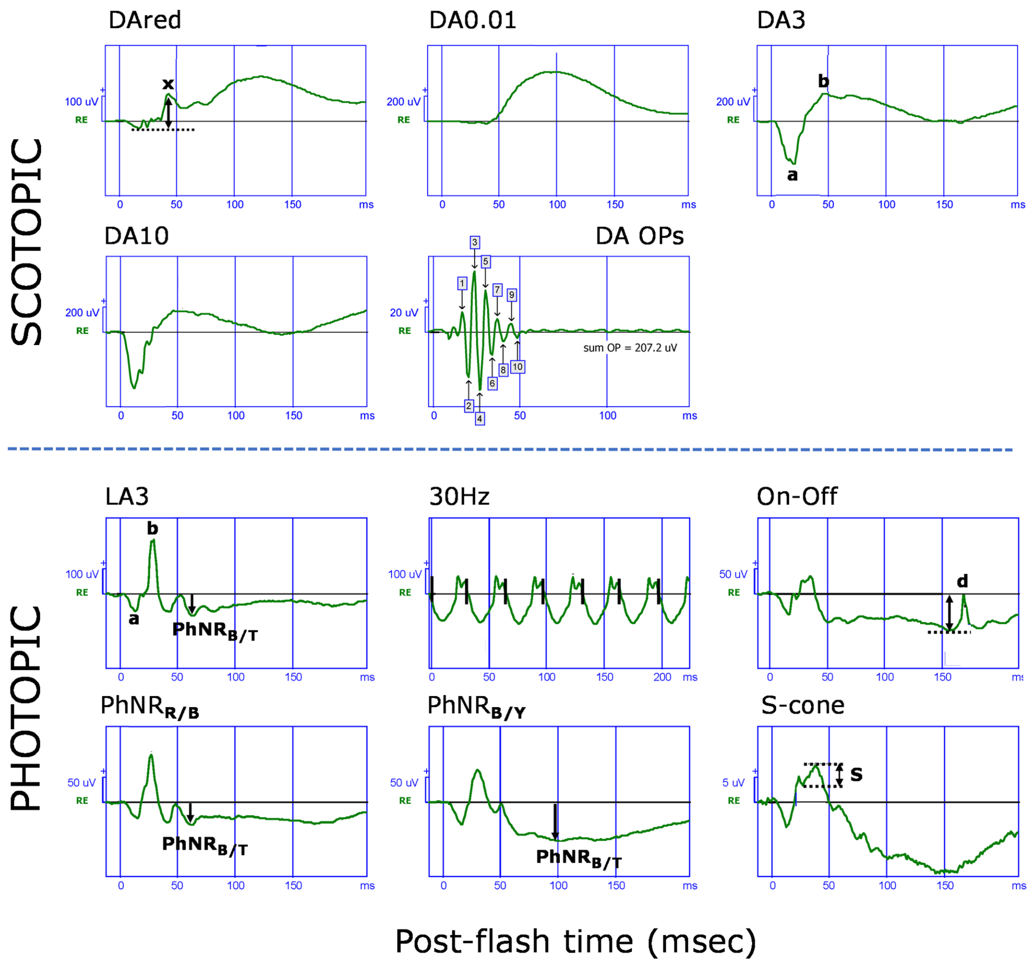

Figure 2. Representative ffERGs recorded from a 24-year-old man. For clarity, ERG a- and b-wave amplitudes shown only for DA3 and LA3. DA red x-wave was measured relative to the preceding trough (a-wave). PhNR measurements shown were made relative to baseline (PhNR$_{BT}$); PhNR amplitude relative to the peak of the b-wave was also made (PhNR$_{PT}$; not shown). The amplitude of the d-wave (d) of the ON–OFF response was made from the preceding trough; d-wave implicit time was measured relative to light offset at 150 ms. S-cone amplitude (S) was measured from the second peak to the preceding trough. Numbers after DA and LA refer to flash strength (cd-s/m^2). DA, dark adapted; LA, light adapted; PhNR, photopic negative response to a red-on-blue stimulus (PhNR$_{R/B}$) or blue-on-yellow stimulus (PhNR$_{B/Y}$).

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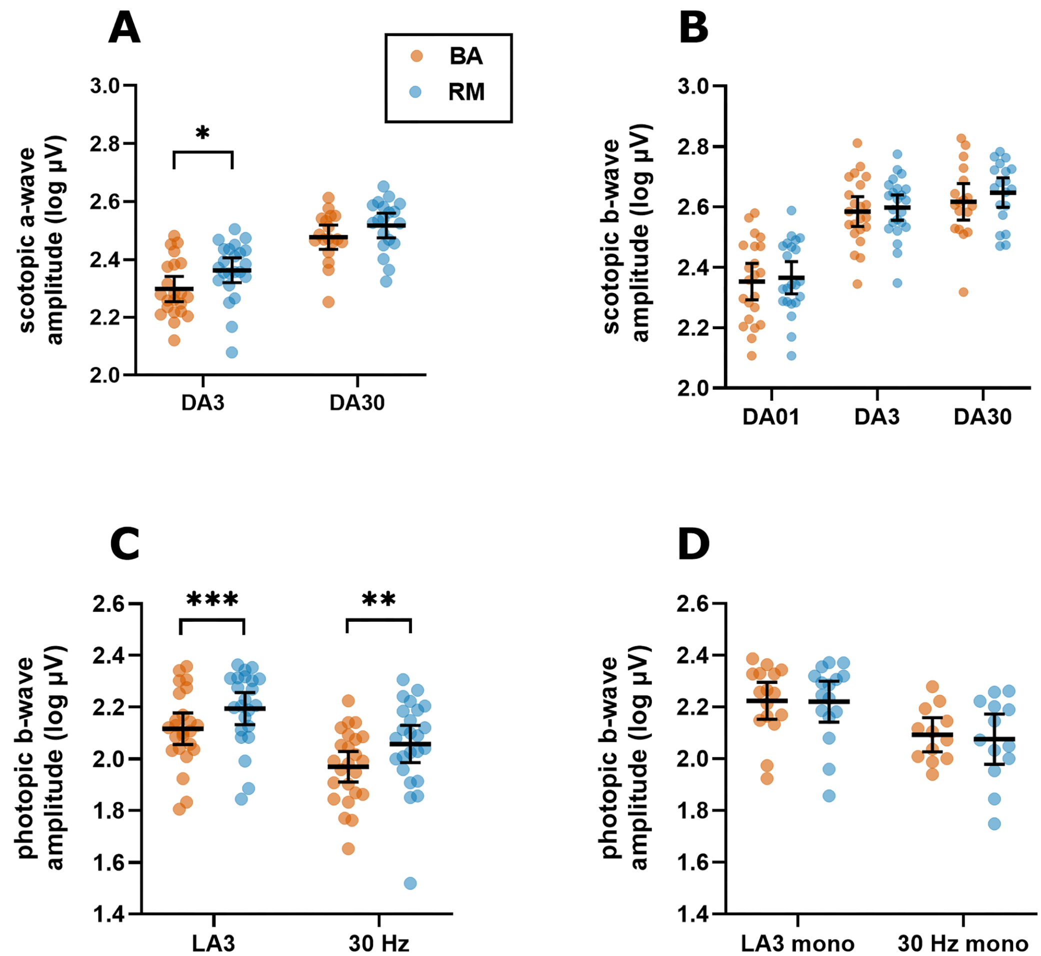

Figure 3. Comparison of ERG amplitudes from BA (*orange*) and RM Electrodes (*blue*). Scotopic a-wave and b-wave amplitudes are compared in panels (**A**) and (**B**), respectively. (**C**) Photopic b-wave amplitude comparisons. (**D**) Photopic b-wave amplitudes recorded from the BA and RM Electrodes in a monopolar configuration (i.e., referenced to a skin electrode on the ipsilateral outer canthus). Adjusted comparisons: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. *Horizontal line* and *error bars* indicate mean ± 95% CI. Numbers after DA and LA refer to flash strength (cd-s/m^2). DA, dark adapted; LA, light adapted; mono, monopolar configuration.

(Supplementary Tables S6). For all other photopic ERG amplitudes (b-wave, PhNR PT, and ON–OFF), we accepted the null hypothesis that these parameters followed a Gaussian (normal) distribution (Supplementary Table S6). All implicit times followed log-normal distributions (Supplementary Tables S7 and S8). These parameter distributions were used for the ERG comparisons and ERG reference ranges described below.

Comparison of ERG Parameters Between BA and RM Electrodes

ERG parameters were compared between the two electrodes using their intended configurations (i.e., the RM Electrode as a monopolar and the BA as a bipolar electrode). DA3 a-wave amplitudes (log mean ± SD; linear mean) from the RM Electrode (2.368 ± 0.100 log µV; 233 µV) were 18% larger (adjusted $P = 0.02$) than the BA electrode (2.298 ± 0.099 log µV; 199 µV) (Fig. 3A). A similar trend was noted for the DA30 a-waves, although the difference between the two electrodes (11%) did not reach significance ($P = 0.07$, Fig. 3A). There were no significant differences in scotopic b-wave amplitudes between the RM Electrode and BA electrode (Fig. 3B).

Photopic amplitudes (Fig. 3C) from the RM Electrode (LA3 = 2.195 ± 0.144 log µV; 157 µV and 30 Hz = 2.057 ± 0.171 log µV; 114 µV) were 20% ($P < 0.001$) and 22% ($P = 0.002$) larger compared with the BA electrode (LA3 = 2.116 ± 0.144 log µV; 131 µV and 30 Hz = 1.97 ± 0.140 log µV; 93 µV).

To examine the effect of the difference in configurations, we switched the BA to a monopolar configuration (referenced to the outer canthus) at the

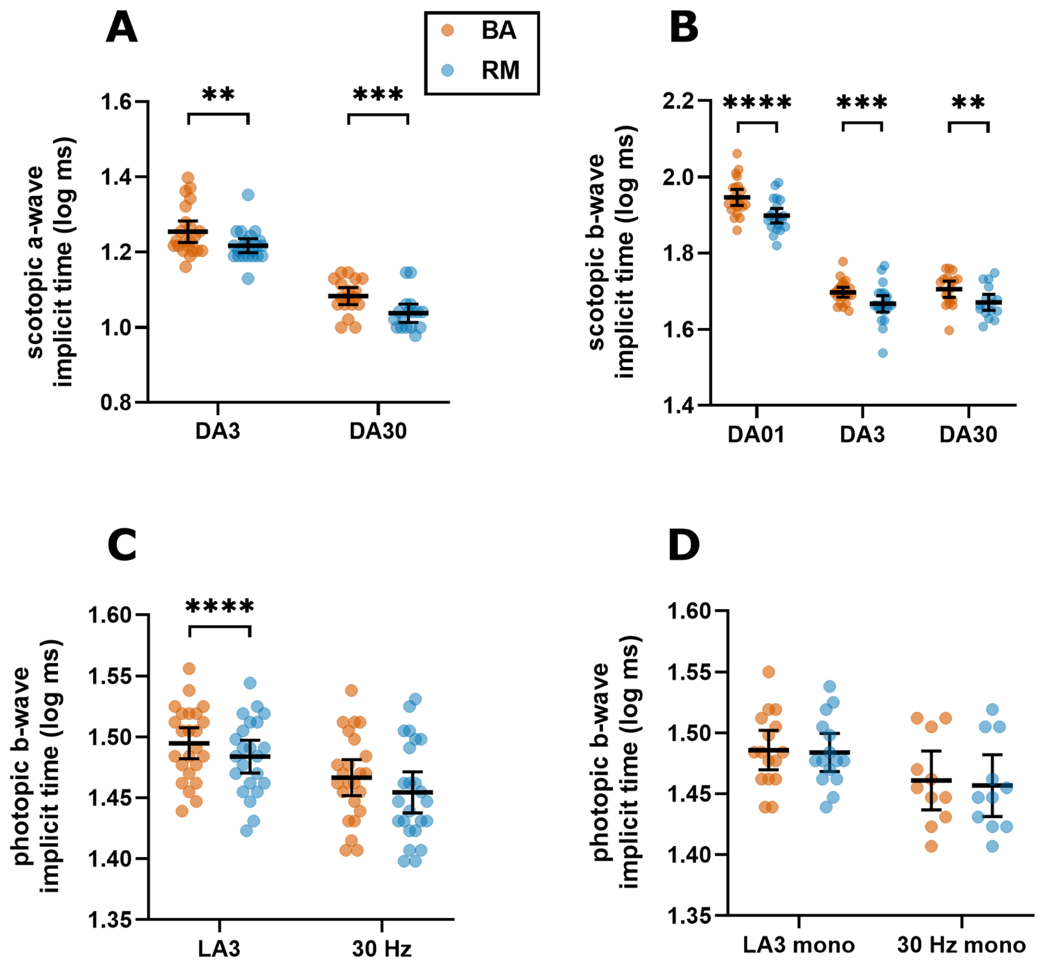

Figure 4. Comparison of ERG implicit times from BA (*orange*) and RM Electrodes (*blue*). Scotopic a-wave and b-wave implicit times are compared in panels (**A**) and (**B**), respectively. (**C**) Comparison of photopic b-wave implicit times. (**D**) Photopic b-wave implicit times recorded from the BA and RM Electrodes in a monopolar configuration (i.e., referenced to a skin electrode on the ipsilateral outer canthus). Adjusted comparisons: $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. *Horizontal line* and *error bars* indicate mean ± 95% CI. Numbers after DA and LA refer to flash strength (cd-s/m^2).

end of the photopic session. We then repeated the LA3 and 30-Hz recordings. When both electrodes were used in a monopolar configuration, there were no significant differences in photopic amplitudes (Fig. 3D).

ERG implicit times were also compared across the two electrodes (Fig. 4). Implicit times from the bipolar BA were significantly longer compared to the RM Electrodes for all scotopic recordings (Figs. 4A, 4B) and for the LA3 b-wave (Fig. 4C). The largest difference occurred for the DA01 b-wave, which on average was 9.2 ms longer (12%; $P < 0.0001$) from the BA electrode (Fig. 4B). ERG a-wave and b-wave implicit times were longer from the BA electrode by 1.3 ms (7.6%) and 3.5 ms (10.8%) for the scotopic a-waves and b-waves, respectively (Figs. 4A, 4B). LA3 implicit time from the bipolar BA was slightly but significantly longer from the BA electrode (0.9 mc [3%]; $P < 0.0001$; Fig. 4C). As above, when ERGs were recorded from both electrodes used in a monopolar configuration, photopic implicit times were not significantly different (Fig. 4D).

Comparison of ERG Recording Stability Between BA and RM Electrodes

The stabilities of the ERGs recorded from the two electrodes were compared using %CV. The %CV was calculated from the ratio of the standard deviation of the amplitudes of individual responses relative to the mean amplitude (see Methods). The higher the %CV, the higher the variability of each individual ERG response. The %CV was not normally distributed, and electrodes were compared using the nonparametric Wilcoxon matched-pairs signed rank test.

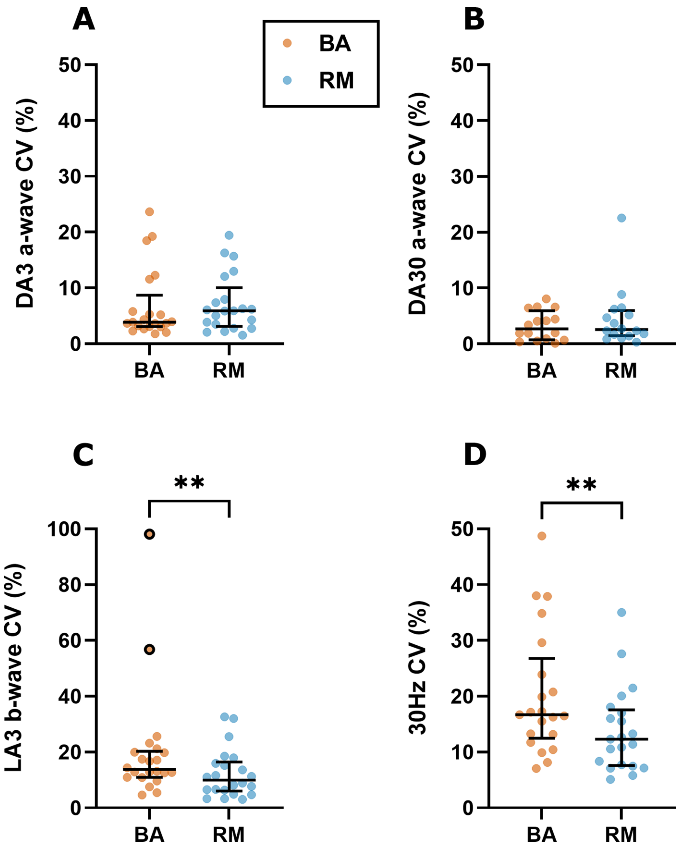

Figure 5. Coefficients of variation of ERG amplitudes from BA (*orange*) and RM Electrodes (*blue*). CVs for the scotopic DA3 and DA30 a-wave amplitudes are shown in panels (**A**) and (**B**), respectively. (**C**) CVs for photopic LA3 amplitudes. *Orange symbols* with *black circles* indicate outliers. (**D**) CVs for 30-Hz amplitudes. Wilcoxon matched-pairs signed rank test: $^{**}P < 0.01$. *Horizontal line* and *error bars* indicate median with interquartile range. Numbers after DA and LA refer to flash strength (cd-s/m^2).

There were no significant differences in ERG stability between the RM Electrode and BA electrode for either the DA3 a-wave (Fig. 5A: median [interquartile range] %CV for RM Electrode = 5.9 [3.1–10.0] vs. BA = 3.9 [3.1–8.7]) or the DA30 a-wave (Fig. 5B: %CV for RM Electrode = 2.5 [1.5–6.0] vs. BA = 2.7 [0.7–5.9]). Similarly, there were no differences in the stabilities of scotopic ERG b-waves between the two electrodes (Supplementary Fig. S3). Notably, DA30 ERG a- and b-waves were more stable compared with the DA3 ERGs for both electrodes (Fig. 5 and Supplementary Fig. S3).

LA3 ERGs were more stable when recorded from the RM Electrode. For the LA3 b-wave, the %CV for the RM Electrode of 10.0% [6.0–16.4] was significantly lower compared with the BA electrode %CV of 13.8% [10.9–20.3] (P = 0.009; Fig. 5C). Even after excluding the two BA outliers (orange symbols with black circles), the revised %CV for the BA (13.0% [10.9–19.21%]) was still significantly higher than for the RM Electrode ($P = 0.03$).

The 30-Hz flicker ERGs were also more stable from the RM Electrode: %CV = 12.3% [7.6–17.6] compared with the BA electrode: %CV = 16.7% [12.5–26.8] (P = 0.001; Fig. 5D).

Reference Ranges for the RM Electrode

Table 1 summarizes the reference ranges for scotopic and photopic ERG amplitudes that follow log-normal distributions. The achromatic PhNR response ($LA3_{BT}$) and all scotopic amplitudes, except for the red x-wave and DA10 b-wave amplitudes, were correlated with age. Given the variation with age for many parameters, and for ease of interpretation, linear equivalents for means and lower limits are shown in Table 1 for a nominal age of 40 years, the mean age in our study.

Table 1 shows a mean DA3 b-wave amplitude of 489 µV with a lower limit of the normal reference range as 328 µV. However, the 90% CI for this lower limit is 294 to 367 µV (see brackets). A practical use of the 90% CI is to provide a range of amplitudes whose interpretation might be considered indeterminate (i.e., we cannot be certain whether a DA3 b-wave amplitude within the 90% CI is normal or abnormal).

Table 1 also highlights the differing rates of reduction in ERG amplitudes with age. As a reference for using the RM Electrode in the clinic, the means, lower limits, and 90% CIs of all ISCEV standard ffERG amplitudes, as a function of age, are given in Supplementary Table S9.

The reference ranges for the log DA red x/b ratio and scotopic log ERG b/a ratios are shown in Table 2. Since none of these ratios correlated with age, the lower limits (and associated 90% CIs) shown can be adopted for clinical use for any age group.

Table 3 summarizes the reference ranges for photopic ERG amplitudes that followed a normal distribution. The LA3 white-on-white stimulus produced the largest b-wave and PhNR PT amplitudes (Table 3, Supplementary Fig. S4). By comparison, the blue-on-yellow stimulus produced significantly larger PhNR BT amplitudes and BT/b-wave ratios compared with either white-on-white or red-on-blue stimuli (Fig. 6; Tables 1 and 2).

All LA3 amplitude parameters were correlated with age (Tables 1 and 3). None of the other photopic ERG amplitude parameters (except for PhNR blue-on-yellow b-wave) varied with age, nor did the photopic ERG BT/b-wave ratios (Tables 1–3).

Table 4 summarizes the reference ranges for ERG implicit times, which all follow log-normal

Table 1. Reference Ranges of Scotopic and Photopic Amplitudes With Log-Normal Distributions

ERG Component	N	Correlation With Age (R^2)	Mean ± SD (Log μV)	Mean 40 Y (μV)	Lower Limit at 40 y (μV) [±90% CI]	Amplitude Reduction Per Decade (%/dec)
Scotopic						
DA red						
x-wave	32	NS	2.110 ± 0.153	129	72 [60–86]	—
b-wave	30	$P = 0.013$ (0.20)	2.148 ± 0.222	141	61 [47–79]	14.7
DA01						
b-wave	37	$P < 0.0001$ (0.36)	2.456 ± 0.152	286	161 [137–189]	12.2
DA3						
a-wave	38	$P = 0.006$ (0.19)	2.439 ± 0.123	275	172 [151–196]	7.4
b-wave	38	$P = 0.050$ (0.10)	2.689 ± 0.105	489	328 [294–367]	4.6
DA10						
a-wave	37	$P = 0.029$ (0.13)	2.538 ± 0.115	346	224 [198–253]	5.8
b-wave	37	NS	2.699 ± 0.111	500	329 [292–370]	—
OPs						
sum	33	$P < 0.0001$ (0.44)	2.178 ± 0.234	151	62 [48–81]	20.9
Photopic						
LA3						
BT	39	$P = 0.001$ (0.25)	1.750 ± 0.186	43	21 [17–25]	12.8
$PhNR_{R/B}$						
BT	32	NS	1.512 ± 0.173	33	17 [14–21]	—
$PhNR_{B/Y}$						
BT	23	NS	1.806 ± 0.227	64	27 [20–37]	—
S-cone						
s-cone	26	NS	0.773 ± 0.204	5.9	2.7 [2.1–3.5]	—

BT, baseline to trough; DA, dark adapted; LA, light adapted.

Table 2. Reference Ranges of Scotopic and Photopic Amplitude Ratios

ERG Component	N	Correlation With Age (R^2)	Mean Log Ratio ± SD	Mean Ratio	Lower Limit [±90% CI]
Scotopic					
DA red					
x/b ratio	30	NS	−0.077 ± 0.166	0.84	0.45 [0.37–0.54]
DA3					
b/a ratio	38	NS	0.252 ± 0.074	1.79	1.35 [1.25–1.46]
DA10					
b/a ratio	37	NS	0.157 ± 0.052	1.44	1.18 [1.12–1.25]
Photopic					
LA3					
BT/b-wave	39	NS	−0.618 ± 0.193	0.24	0.12 [0.09–0.14]
$PhNR_{R/B}$					
BT/b-wave	31	NS	−0.506 ± 0.171	0.31	0.16 [0.13–0.20]
$PhNR_{B/Y}$					
BT/b-wave	22	NS	−0.108 ± 0.165	0.78	0.42 [0.33–0.52]

Table 3. Reference Ranges of Photopic Amplitudes With Normal Distributions

ERG Component	N	Correlation With Age (R^2)	Mean ± SD at 40 y (µV)	Lower Limit at 40 y (µV) [±90% CI]	Amplitude Reduction Per Decade (%/dec)
Photopic					
LA3					
b-wave	39	$P = 0.022$ (0.13)	185 ± 52	100 [76–123]	12.1
PT	39	$P = 0.010$ (0.16)	183 ± 51	99 [76–122]	12.7
30Hz					
b-wave	39	NS	145 ± 49	65 [43–87]	—
$PhNR_{R/B}$					
b-wave	32	NS	111 ± 38	49 [30–67]	—
PT	31	NS	119 ± 40	53 [33–74]	—
$PhNR_{B/Y}$					
b-wave	23	$P = 0.030$ (0.21)	81 ± 32	29 [10–47]	10.8
PT	22	NS	124 ± 47	47 [19–75]	—
ON–OFF					
b-wave	36	NS	75 ± 28	29 [16–42]	—
d-wave	33	NS	55 ± 25	15 [2–27]	—

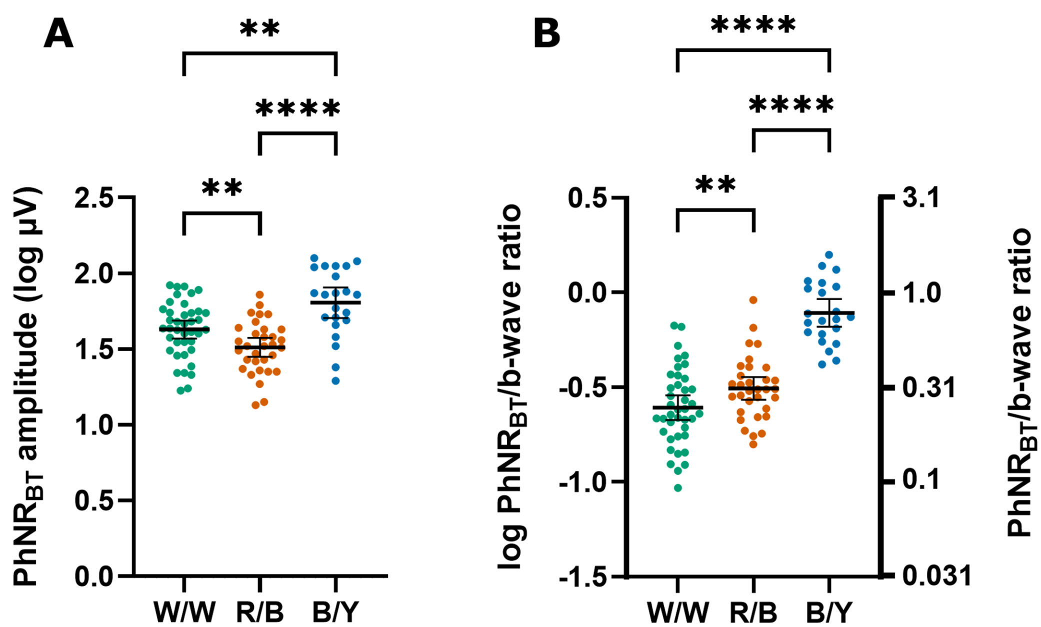

Figure 6. Comparison of log PhNR baseline-to-trough ($PhNR_{BT}$) amplitudes (**A**) and log $PhNR_{BT}$/b-wave ratios (**B**). For both comparisons, the mixed-effects models were significant ($P < 0.0001$) for the main factor of stimulus type (W/W = white-on-white, R/B = red-on-blue, B/Y = blue-on-yellow). Post hoc comparisons: $^{**}P < 0.01$, $^{****}P < 0.0001$. *Horizontal line* and *error bars* indicate mean ± 95% CI.

distributions. As above, linear equivalents for means and upper limits are shown in Table 4 for a nominal age of 40 years. Scotopic a-waves but not b-wave implicit times correlated with age (Table 4). The cone-mediated DA red x-wave and all photopic b-waves, except LA3, were correlated with age.

As a reference for using the RM Electrode in clinic, the means, lower limits, and 90% CIs of all ISCEV standard ffERG implicit times as a function of age are given in Supplementary Table S10.

Discussion

The ffERG is widely used in ophthalmology clinics for the diagnosis and management of retinal

Table 4. Reference Ranges of Implicit Times With Log-Normal Distributions

ERG Component	N	Correlation With Age (R^2)	Mean ± SD (Log ms)	Mean at 40 Y (ms)	Upper Limit at 40 y (ms) [±90% CI]	Implicit Time Increase Per Decade (ms/dec)
Scotopic						
DA red						
x-wave	32	$P = 0.036$ (0.14)	1.680 ± 0.034	47.9	54.4 [52.3, 56.5]	0.92
b-wave	30	NS	2.078 ± 0.059	119.7	150 [140–161]	—
DA01						
b-wave	37	NS	1.971 ± 0.040	93.5	109 [104–114]	—
DA3						
a-wave	36	$P = 0.007$ (0.29)	1.307 ± 0.018	20.3	21.8 [21.3–22.2]	0.29
b-wave	38	NS	1.695 ± 0.032	49.5	56.0 [54.2, 58.0]	—
DA10						
a-wave	37	$P = 0.001$ (0.49)	1.041 ± 0.042	11.0	12.9 [12.3–13.5]	0.16
b-wave	37	NS	1.712 ± 0.050	51.5	62.3 [59.1–65.8]	—
Photopic						
30HZ						
b-wave	39	$P = 0.001$ (0.25)	1.402 ± 0.036	25.3	29.0 [27.9–30.1]	0.68
LA3						
b-wave	39	NS	1.454 ± 0.023	28.4	31.0 [30.3–31.8]	—
PhNR	38	$P = 0.040$ (0.11)	1.7 ± 0.026	62.9	69.4 [67.6–71.4]	0.79
$PhNR_{R/B}$						
b-wave	32	$P = 0.007$ (0.22)	1.454 ± 0.034	28.4	32.3 [31.1–33.6]	0.68
PhNR	32	$P = 0.022$ (0.16)	1.810 ± 0.038	64.6	74.7 [71.5–78.0]	1.51
$PhNR_{B/Y}$						
b-wave	23	$P = 0.012$ (0.40)	1.526 ± 0.037	33.6	38.6 [36.8–40.6]	1.38
PhNR	23	NS	2.026 ± 0.079	106.2	143 [129–160]	—
ON–OFF						
b-wave	36	$P = 0.007$ (0.20)	1.521 ± 0.053	33.2	40.6 [38.4–43.0]	1.21
d-wave	33	$P = 0.018$ (0.17)	1.340 ± 0.030	21.9	24.6 [23.8–25.4]	0.80
S-cone						
S-cone	26	NS	1.586 ± 0.022	38.5	41.9 [40.7–43.0]	—

disease. There is a long history of developing different electrodes for recording the human ERG.[4] Each electrode iteration has sought to overcome limitations related to signal amplitude and stability, optical clarity, photo-voltaic artifact, comfort, and sterilization, among the major issues addressed.

The RM Electrode is single-use (shipped sterile), which obviates issues surrounding sterilization. The RM Electrode has lower interflash variability for photopic ERGs, which may stem from the way in which each electrode is held against the eye. The RM Electrode incorporates two base curves to conform closely to the cornea and anterior sclera, which holds the electrode against the eye and enables the electrode to move with the eye. By comparison, the BA electrode uses a speculum to hold the electrode in place and keep the eyelids open, but the eye can still move. We speculate that under photopic conditions, the participants blink more and the resulting movement of the BA electrode across the eye is associated with greater voltage drift than observed with the RM Electrode.

To our knowledge, the data provided herein are the first human normative reference range for the RM Electrode, collected in accordance with the ISCEV standard ffERG and several extended protocols. Importantly, we have recruited from a population that provides representation of the US population reported in the 2020 Census (www.census.gov: race: white = 66%; black = 13%; Asian = 16%; ethnicity: Hispanic = 19%).

The results presented here indicate that the RM Electrode produces the same amplitudes and implicit times as a monopolar BA electrode. For laboratories with bipolar BA normative data, our results suggest scaling scotopic a-wave and photopic amplitude ranges by a factor of 1.2 when adopting the RM Electrode; scotopic b-wave amplitude ranges will not change. Our comparison of the two electrodes is further supported by previous studies using BA electrodes (Supplementary Tables S11 and S12). The mean values of DA01 and DA3 b-wave amplitudes from the RM Electrode (Table 1: 286 µV and 489 µV, respectively) are similar to studies using bipolar BA electrodes (Supplementary Tables S11, Supplementary references SR1, SR3, SR4). By comparison, the mean LA3 b-wave of the RM Electrode (185 µV) is 13% to 35% (median = 25%) larger than for the bipolar BA electrode from these same studies. Implicit times for the RM Electrode are also similar to previous reports that used BA electrodes (Supplementary Table S12). Birch and Anderson[11] reported smaller ERG amplitudes and faster implicit times from their bipolar BA recordings (Supplementary Table S11, Supplementary reference SR2). However, they used a much narrower filter bandwidth (2–300 Hz) than used here and in the other studies in Supplementary Table S11; the ffERG has substantial energy below 2 Hz.[26,27]

The RM Electrode reference ranges for the ISCEV extended protocols are compared with other electrodes in supplemental data as follows: dark-adapted red flash (Supplementary Table S13), the photopic negative response (Supplementary Tables S14 and S15), the photopic ON–OFF ERG (Supplementary Table S16), and the S-cone ERG (Supplementary Table S17). Given that most reports in these supplemental tables were published before 2018, we only included reports that used stimulus conditions close to those specified by the ISCEV extended protocols (published 2018–2020). We focused our comparison of the RM Electrode to previous studies using CLEs. We included some non-CLEs studies for two reasons: (1) non-CLE studies with large numbers of participants over a wide age range or (2) for comparison when there were a small number of CLE studies (e.g., PhNR and S-cone).

Comparison of absolute amplitudes between the RM Electrode and other electrodes across the ISCEV extended protocols largely mirrors the results above for the ISCEV ffERG standard. The RM Electrode has comparable amplitudes to monopolar CLEs for PhNR[SR11], ON–OFF[SR19,SR20], and S-cone[SR26] (Supplementary Tables S15, S16, and S17, respectively). Additionally, the RM Electrode produces larger amplitudes compared with bipolar CLEs with photopic ON–OFF ERGs[SR18,SR21] (Supplementary Table S16) and DTL electrodes for PhNR and ON–OFF ERGs (Supplementary Tables S14 and S16). By comparison, S-cone amplitudes vary greatly across studies, regardless of the electrode type used (Supplementary Table S17). For all but one study, S-cone ERGs are small, with an average amplitude less than 6 µV.

In the current study, the PhNR response to the blue-on-yellow stimulus was significantly larger than for the white-on-white stimulus; both were significantly larger than the red-on-blue stimulus. Our results mirror those of Kremers et al.,[28] who, in a detailed spectral analysis of the PhNR, found the largest response occurred for a blue-on-yellow stimulus.

The variation in ERG amplitudes and implicit times with age reported herein is largely in agreement with other studies (Supplementary Tables S11–S17). For the ISCEV standard ffERG studies, scotopic ERG and LA3 amplitudes decrease with age, while 30-Hz amplitude does not (Supplementary Table S11). A large study of 269 healthy volunteers did find a significant increase in DA3 and LA3 b-wave implicit times with age[SR11]; smaller studies did not find such correlations, implying a small effect or underpowered studies (Supplementary Table S11).

A notable result is that cone-mediated amplitudes do not vary with age for any of the ISCEV extended protocols summarized in supplemental data (see Supplementary Tables S13–S17). Fewer studies examined the effect of age on implicit time than on amplitude. This small number of studies suggests that cone-mediated implicit time varies with age for the red-on-blue PhNR and ON–OFF ERGs (Supplementary Tables S14 and S16) but not for the blue-on-yellow PhNR or S-cone ERG (Supplementary Tables S15 and S17).

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Appendix

The following information was provided by Drs. John Hetling and Shresta Patangay from RetMap.

The RM Electrode was designed with the main goals of improving comfort and repeatability while reducing motion artifact due to blinking in a single-use disposable electrode.

Features of the Electrode:

- Soft: The eye-contact portion (substrate) of the RM Electrode is made of soft medical-grade silicone for comfort and safety.
- Double base curve: The RM Electrode has a double base curve that conforms to the cornea and sclera to maintain positional stability.
- Recessed electrode: The active electrode is a gold-plated electrode that makes indirect electrical contact through the conductive fluid layer (mix of ophthalmic lubricating solution and natural tears) to reduce motion artifacts.
- Integral speculum: The speculum (also soft) is integral to the substrate and retracts the eyelids for consistent pupil exposure. It also helps prevent the wearer from blinking during ERG testing. Avoiding blinking during ERG testing is important to help reduce electrical motion and blink artifacts.

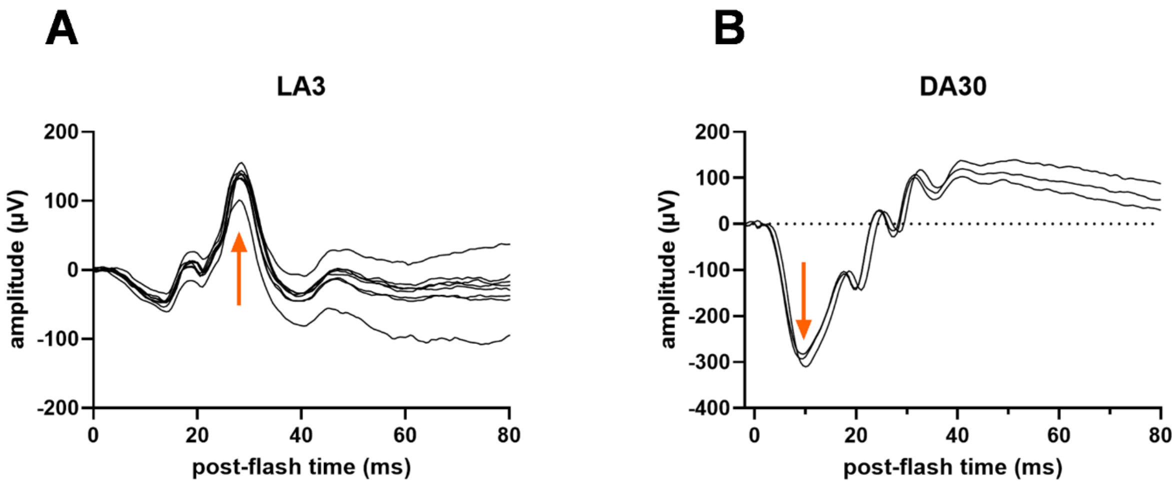
Safety and Use

- The RM Electrode is FDA cleared (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K232273). It is indicated for use in patients aged 12 years and above undergoing diagnostic ffERG recording procedures. The current version of the RM Electrode is not optically clear and, therefore, not suitable for pattern ERG or multifocal ERG (mfERG).

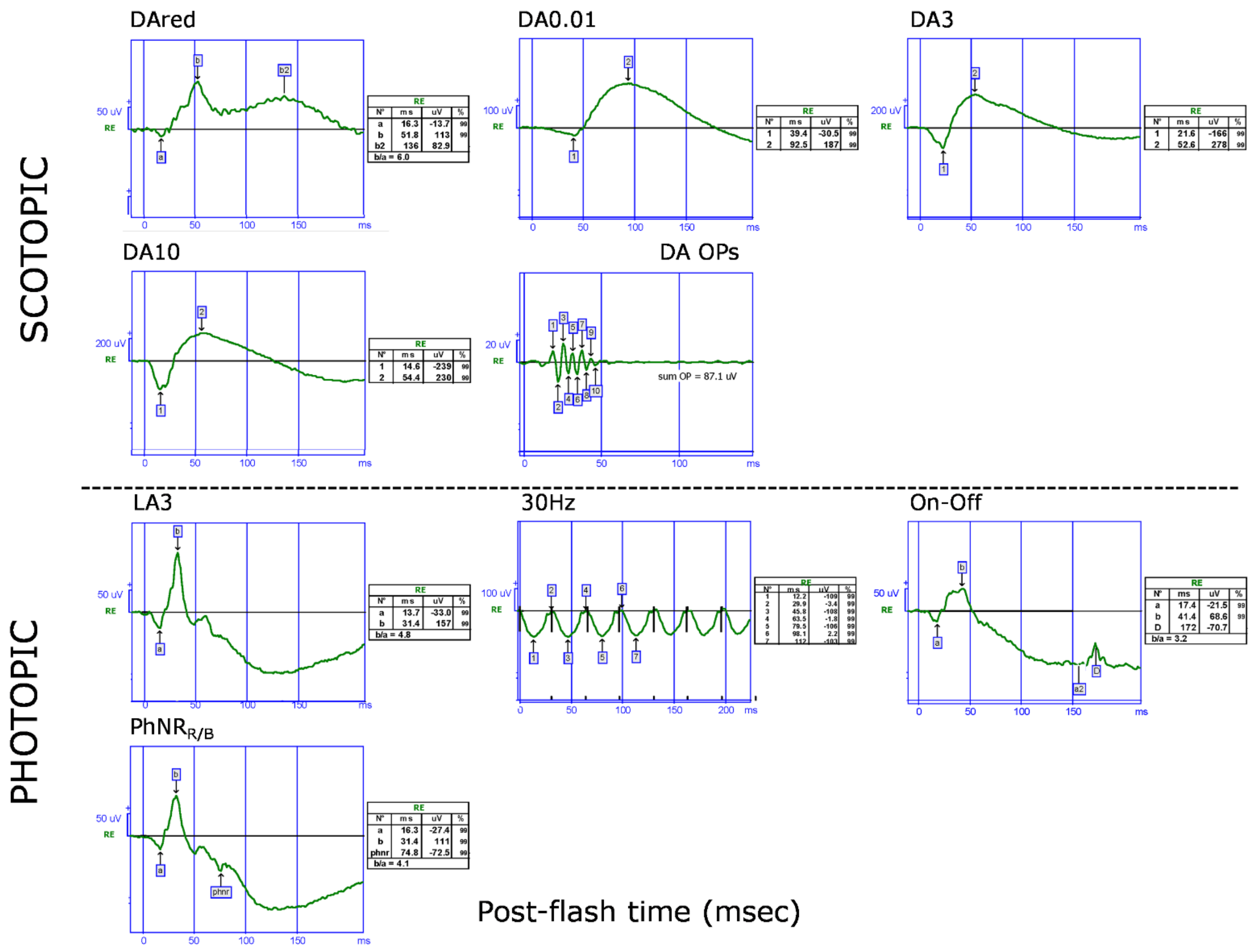
Comfort:

- Limbal, bulbar, and tarsal redness were compared from the eyes of 10 healthy adults wearing an RM Electrode in one eye and an ERG-Jet electrode in the contralateral eye (Patangay S. *IOVS*. 2024;65:ARVO E-Abstract 5851).
  - After 20 minutes of wear, limbal redness was significantly higher in the eyes wearing the ERG-Jet electrode.
  - After 40 and 60 minutes of wear, both limbal and bulbar redness were significantly higher in the eyes wearing the ERG-Jet electrode.
  - There was no difference in tarsal redness between eyes (electrode type) at any time point.

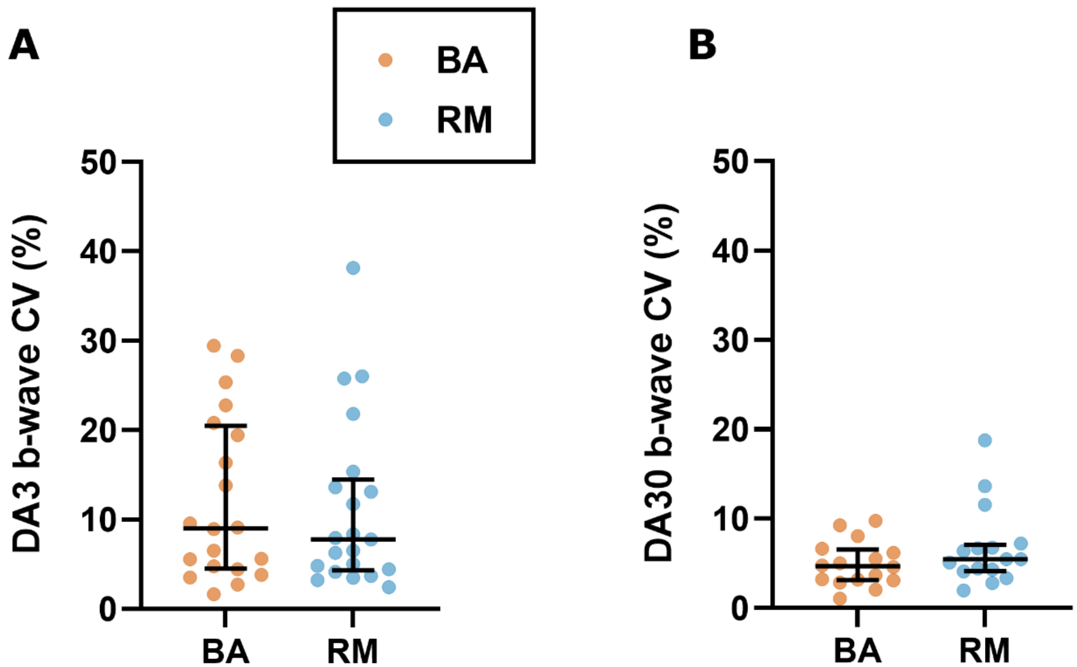
Supplemental Data



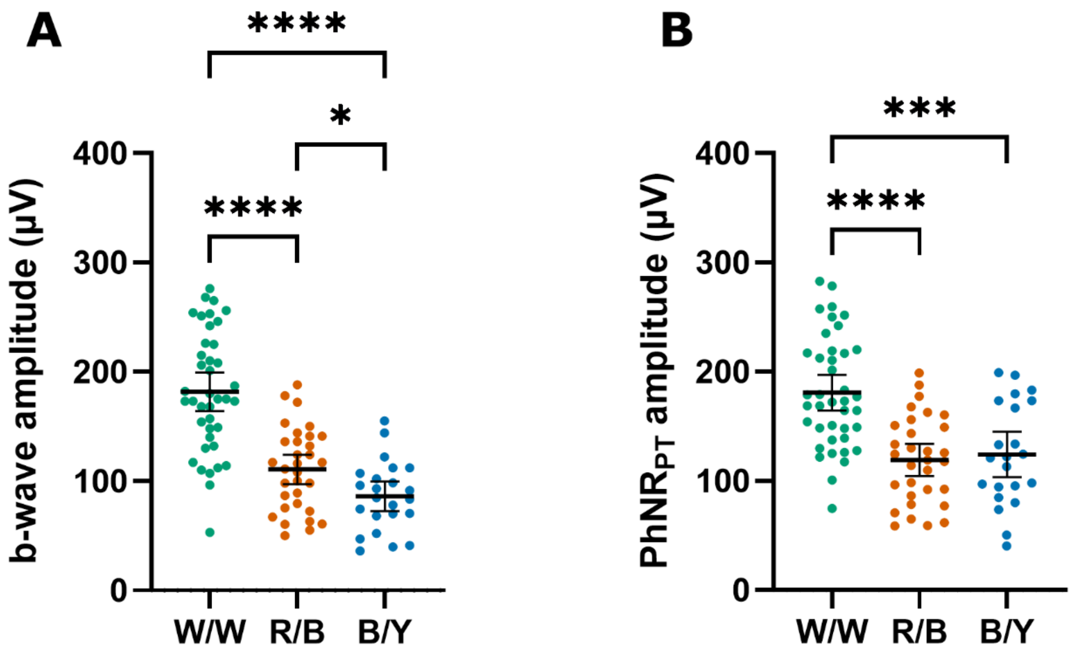
Supplementary Figure S1: Quantifying variability of ERGs. Variability was quantified by calculating the coefficient of variability (CV), defined as the ratio of standard deviation to the mean and expressed as a percentage. (**A**) Individual ERG traces from a BA electrode recorded for LA3 (n = 8 traces). ERG b-wave amplitudes were measured from baseline at time zero to the peak of the b-waves (upward orange arrow). Mean = 134.7 µV; SD = 24.7 µV; CV= 18.3% (**B**) Individual ERG traces from a RM electrode recorded for DA30 (n = 3 traces). ERG a-wave amplitudes were measured from the baseline at time zero to the trough of the a-waves (downward orange arrow). Mean = 294.9 µV; SD = 18.4 µV; CV= 6.2%



Supplementary Figure S2: Representative ffERGs recorded from a 74yo female, the oldest participant in our study. ERG a-wave and b-wave amplitudes and implicit times were made according to the ISCEV ERG standards and Extended ERG protocols. The PhNR measurements shown were made relative to baseline (PhNR$_{BT}$); we also calculated PhNR amplitude relative to the peak of the b-wave (PhNR$_{PT}$; not shown). 30Hz amplitude was measured from the average of the peak to trough amplitude differences (i.e. points 1-2, 3-4, 5-6). 30Hz implicit time (IT) was calculated from the mean of flash onset (vertical black lines) to the peaks of the responses. (Nº2 IT = 29.9 ms; Nº4 IT = 63.5-33 = 30.5ms, etc) The amplitude of the d-wave of the ON-OFF response was made from the preceding trough (a2) to the peak of the response (D). D-wave implicit time was measured relative to light offset at 150 msec. Abbreviations: DA = dark adapted, LA = light adapted, PhNR = photopic negative response to a red on blue stimulus (PhNR$_{R/B}$). Numbers after DA and LA refer to flash strength (cd-s/m^2).



Supplementary Figure S3: Co-Efficient of Variation of Scotopic ERG b-wave amplitudes from Burian Allen (orange) and RM (blue) electrodes. CVs for the scotopic DA3 and DA30 b-wave amplitudes are shown in panels (**A**) and (**B**) respectively. Wilcoxon matched-pairs signed rank test comparisons: no significant differences. Horizontal line and error bars indicate median with interquartile range. Abbreviations: BA = Burian-Allen, DA = dark adapted, CV = coefficient of variation. Number after DA refers to flash strength (cd-s/m^2).



Supplementary Figure S4: Comparison of photopic b-wave amplitudes (**A**) and PhNR peak-to-trough (PhNR PT) amplitude (**B**). For both comparisons, the mixed effects models were significant (P<0.0001) for the main factor of stimulus type (W/W = white-on-white, R/B = red-on-blue, B/Y = blue-on-yellow). Post-hoc comparisons: *P<0.05; ***P<0.001; ****P<0.0001. Horizontal line and error bars indicate mean ± 95% CI. Abbreviations: PT = peak to trough; PhNR = photopic negative response.

Supplemental Table S1: ERG recording specifications on LKC for ISCEV Standard ERGs

ISCEV Stimulus	Number of responses averaged	Interstimulus interval (sec)	Artifact rejection level (μV)	Display scale (μV)
DA0.01	5	5	1500	+/- 250
DA3	3	10	1500	+/- 500
OPs DA3	3	15	1500	+/- 500
DA30	3	20	2000	+/- 250
LA3	8	3	800	+/- 125
LA 30Hz	20	0.033	500	+/- 125

*All recordings made with bandpass filter (0.3 – 500 Hz). Notch filtering was not used.

Supplemental Table S2: ERG recording specifications on MonCvONE for ISCEV Standard ffERGs

ISCEV Stimulus	Number of responses averaged	Interstimulus interval (msec)	Artifact rejection level (μV)	Stimulus strength (ph cd-s/m^2)	Background	Gain
DA0.01	5	5003	600	0.01 (5 ms)	white	31.25
DA3	3	10005	800	2.82(5 ms_	white	31.25
DA10	3	20005	800	8.49 (5 ms)	white	31.25
OPs (DA3)	3	15005	230	2.82 (5 ms)	white	12500
LA3	10	3002	750	2.82	white	12 500
LA 30Hz	20	0.033	750	2.82	white	12500

*Notch filtering was not used.

Bandpass = 0.1 – 329 Hz; except OPs: bandpass = 100-329 Hz; Photopic background = achromatic = 28.3 cd/m2;

Supplemental Table S2: ERG recording specifications on MonCvONE for ISCEV Extended Protocols

ISCEV Stimulus	Number of responses averaged	Interstimulus interval (msec)	Artifact rejection level (μV)	Stimulus strength (ph cd-s/m^2)	Stimulus dominant wavelength (nm)	Background (ph cd/m^2)	Background dominant wavelength (nm)
DA red	10	4003	500	0.283	655	0	N/A
ON-OFF#	30	1283	600	37.8	achromatic	28.3	achromatic
$PhNR_{R/B}$	30	1003	544	1.42	655	7.99	455
$PhNR_{B/Y}$	30	1003	500	0.09	455	10.1	591
S-Cone	300	4001	500	0.05	455	321	591

*Notch filtering was not used. #Background ON Duration =150 msec;

Bandpass = 0.1 -329 Hz for all stimuli in Suppl Table 2; Gain = 12 500 for extended photopic; Gain = 31.25 for DA red. All stimuli were 5 msec duration except ON/OFF where stimulus on for 150 msec

Supplemental Table S4: Number of Participants by Age and Gender

Age (years)	Male	Female	Total
20-29	8	6	14
30-39	6	3	9
40-49	1	4	5
50-59	4	4	7
60-69	2	2	4
>70	0	1	1

Supplemental Table S5: Scotopic ERG Amplitude Distributions

ERG Component	N	Probability Gaussian/log Gaussian (%)	Passed Tests for Normality	Passed tests for log Normality	QQPlot best fit	Visible Inspection	Distribution used
DA red							
• x-wave	32	5/95	No	Yes	logNormal	logNormal	logNormal
• b-wave	30	4/96	Yes	Yes	logNormal	logNormal	logNormal
• x/b ratio	30	28/72	Yes	Yes	logNormal	logNormal	logNormal
DA01							
• b-wave	37	10/90	Yes	Yes	logNormal	logNormal	logNormal
DA3							
• a-wave	38	42/58	Yes	Yes	logNormal	logNormal	logNormal
• b-wave	38	10/90	Yes	Yes	logNormal	logNormal	logNormal
• b/a ratio	38	7/93	No	Yes	logNormal	logNormal	logNormal
DA10							
• a-wave	37	62/38	Yes	Yes	Normal	Either	logNormal
• b-wave	37	27/73	Yes	Yes	logNormal	logNormal	logNormal
• b/a ratio	37	31/69	Yes	Yes	logNormal	logNormal	logNormal
OPs							
• sum	33	2/98	Yes	Yes	logNormal	logNormal	logNormal

Supplemental Table S6: Photopic ERG Amplitude Distributions

ERG Component	N	Probability Gaussian/log Gaussian (%)	Passed Tests for Normality	Passed tests for log Normality	QQPlot best fit	Visible Inspection	Distribution used
LA3							
• b-wave	39	60/40	Yes	Yes	Normal	Normal	Normal
• $PhNR_{PT}$	39	25/75	Yes	Yes	logNormal	Normal	Normal
• $PhNR_{BT}$	39	43/57	Yes	Yes	lognormal	Normal	logNormal
• $PhNR_{BT}$/b-wave ratio	39	0/100	No	Yes	lognormal	logNormal	logNormal
LA							
• 30Hz	39	95/5	Yes	No	Normal	Normal	Normal
PhNR (R/B)							
• b-wave	32	57/43	Yes	Yes	Normal	Normal	Normal
• $PhNR_{PT}$	31	55/45	Yes	Yes	Normal	logNormal	Normal
• $PhNR_{BT}$	32	13/87	Yes	Yes	logNormal	logNormal	logNormal
• $PhNR_{BT}$/b-wave ratio	32	0/100	No	No	logNormal	logNormal	logNormal
PhNR (B/Y)							
• b-wave	23	58/42	Yes	Yes	Normal	Normal	Normal
• $PhNR_{PT}$	22	75/25	Yes	Yes	Normal	Normal	Normal
• $PhNR_{BT}$	22	24/76	Yes	Yes	Normal	Normal	logNormal
• $PhNR_{BT}$/b-wave ratio	22	11/89	Yes	Yes	lognormal	logNormal	logNormal
ON-OFF							
• b-wave	36	98/2	Yes	No	Normal	Normal	Normal
• d-wave	33	99/1	Yes	No	Normal	Normal	Normal
S-Cone							
• scone	26	6/94	Yes	Yes	logNormal	logNormal	logNormal

Supplemental Table S7: Scotopic ERG Implicit Time Distributions

ERG Component	N	Probability Gaussian/log Gaussian (%)	Passed Tests for Normality	Passed tests for log Normality	QQPlot best fit	Visible Inspection	Distribution used
DA red							
• x-wave	32	43/57	Yes	Yes	Either	Either	logNormal
• b-wave	30	65/35	Yes	Yes	Either	Normal	logNormal
DA01							
• b-wave	37	46/54	Yes	Yes	Either	Either	logNormal
DA3							
• a-wave	38	49/52	Yes	Yes	Either	Normal	logNormal
• b-wave	38	26/74	No	Yes	logNormal	logNormal	logNormal
DA10							
• a-wave	37	63/37	No	No	Neither	neither	log
• b-wave	37	39/61	Yes	Yes	logNormal	logNormal	logNormal

Supplemental Table S8: Photopic ERG Implicit time Distributions

ERG Component	N	Probability Gaussian/log Gaussian (%)	Passed Tests for Normality	Passed tests for log Normality	QQPlot best fit	Visible Inspection	Distribution used
LA3							
• b-wave	39	39/61	Yes	Yes	logNormal	logNormal	logNormal
• PhNR	39	31/69	No	Yes	logNormal	logNormal	logNormal
LA							
• 30Hz	39	26/74	Yes	Yes	logNormal	Either	logNormal
PhNR (R/B)							
• b-wave	32	33/67	Yes	Yes	logNormal	Normal	logNormal
• PhNR	32	48/52	Yes	Yes	logNormal	Either	logNormal
PhNR (B/Y)							
• b-wave	23	47/53	Yes	Yes	logNormal	Either	logNormal
• PhNR	23	82/18	Yes	Yes	Normal	Normal	logNormal
ON-OFF							
• b-wave	36	53/47	Yes	Yes	Either	Either	logNormal
• d-wave	33	63/37	Yes	Yes	Normal	Normal	logNormal
S-Cone							
• scone	26	40/60	Yes	Yes	Either	logNormal	logNormal

SUPPLEMENTAL TABLE S9: ISCEV ERG AMPLITUDE PARAMETERS (log)

Parameter	DA Red x-wave	DA Red b-wave	DA01	DA3 a-wave	DA3 b-wave	DA10 a-wave	DA10 b-wave	OPs	LA3	30 Hz*
N	32	30	37	38	38	37	37	33	39	39
Slope	-0.003	-0.007	-0.006	-0.003	-0.002	-0.003	-0.002	-0.010	-1.205	-- †
Intercept	2.219	2.424	2.682	2.573	2.772	2.642	2.767	2.586	233.1	145.4
sd	0.153	0.222	0.152	0.123	0.105	0.115	0.111	0.234	51.7	48.7
90% CI	0.076	0.114	0.070	0.056	0.048	0.053	0.051	0.114	23.3	21.9

SUPPLEMENTAL TABLE 9-i: ISCEV ERG MEAN AMPLITUDES BY AGE (LINEAR)

Age (yrs)	DA Red x-wave	DA Red b-wave	DA01	DA3 a-wave	DA3 b-wave	DA10 a-wave	DA10 b-wave	OPs	LA3	30 Hz
20	145	193	371	321	538	389	539	241	209	145
30	135	165	326	297	513	367	518	191	197	145
40	126	141	286	275	489	346	497	151	185	145
50	118	120	251	254	466	326	477	119	173	145
60	110	102	221	235	445	307	458	94	161	145
70	103	87	194	218	424	289	440	74	149	145

SUPPLEMENTAL TABLE 9-ii: ISCEV ERG LOWER LIMIT AMPLITUDES BY AGE

Age (yrs)r	DA Red x-wave	DA Red b-wave	DA01	DA3 a-wave	DA3 b-wave	DA10 a-wave	DA10 b-wave	OPs	LA3	30 Hz
20	81	83	209	201	361	252	354	99	124	65
30	76	71	183	186	344	237	340	78	112	65
40	71	61	161	172	328	224	327	62	100	65
50	66	52	141	159	313	211	314	49	88	65
60	62	44	124	147	299	198	301	39	75	65
70	58	38	109	137	285	187	289	31	63	65

SUPPLEMENTAL TABLE 9-iii: ISCEV ERG: 90% CONFIDENCE INTERVALS OF LOWER LIMIT AMPLITUDES

Age (yrs)	DA Red x-wave	DA Red b-wave	DA01	DA3 a-wave	DA3 b-wave	DA10 a-wave	DA10 b-wave	OPs	LA3	30 Hz
20	68 - 96	64 - 108	178 - 245	176 - 229	323 - 403	223 - 285	315 - 398	76 - 129	100 - 147	43 - 87
30	63 - 90	55 - 92	156 - 215	163 - 212	308 - 384	210 - 268	302 - 383	60 - 102	88 - 135	43 - 87
40	59 - 84	47 - 79	137 - 189	151 - 196	294 - 367	198 - 253	290 - 367	48 - 81	76 - 123	43 - 87
50	55 - 79	40 - 67	120 - 166	140 - 181	280 - 350	186 - 238	279 - 353	38 - 64	64 - 111	43 - 87
60	52 - 73	34 - 57	106 - 146	130 - 168	267 - 333	176 - 224	268 - 339	30 - 50	52 - 99	43 - 87
70	48 - 69	29 - 49	93 - 128	120 - 155	255 - 318	166 - 211	257 - 325	24 - 40	40 - 87	43 - 87

* = linear parameters; † = no correlation with age

SUPPLEMENTAL TABLE S10: ISCEV IMPLICIT TIME PARAMETERS (log)

Parameter	DA Red x-wave	DA Red b-wave	DA01	DA3 a-wave	DA3 b-wave	DA10 a-wave	DA10 b-wave	LA3	30 Hz
N	32	30	37	38	38	37	37	39	39
Slope	0.001	-- †	-- †	0.001	-- †	0.001	-- †	-- †	0.001
Intercept	1.647	2.078	1.971	1.283	1.695	1.017	1.712	1.5	1.4
sd	0.034	0.059	0.040	0.018	0.032	0.042	0.050	0.023	0.036
90% CI	0.017	0.030	0.019	0.009	0.015	0.020	0.023	0.010	0.016

SUPPLEMENTAL TABLE S10-i: ISCEV ERG MEAN AMPLITUDES BY AGE

Age (yrs)	DA Red x-wave	DA Red b-wave	DA01	DA3 a-wave	DA3 b-wave	DA10 a-wave	DA10 b-wave	LA3	30 Hz
20	46.1	119.7	93.5	19.7	49.5	10.7	51.5	28.4	23.9
30	47.0	119.7	93.5	20.0	49.5	10.8	51.5	28.4	24.6
40	47.9	119.7	93.5	20.3	49.5	11.0	51.5	28.4	25.3
50	48.8	119.7	93.5	20.6	49.5	11.2	51.5	28.4	25.9
60	49.7	119.7	93.5	20.9	49.5	11.3	51.5	28.4	26.6
70	50.7	119.7	93.5	21.2	49.5	11.5	51.5	28.4	27.4

SUPPLEMENTAL TABLE S10-ii: ISCEV ERG UPPER LMIT IMPLICIT TIMES BY AGE

Parameter	DA Red x-wave	DA Red b-wave	DA01	DA3 a-wave	DA3 b-wave	DA10 a-wave	DA10 b-wave	LA3	30 Hz
20	52.3	149.7	108.9	21.2	56.0	12.6	62.3	31.0	27.5
30	53.3	149.7	108.9	21.5	56.0	12.7	62.3	31.0	28.2
40	54.4	149.7	108.9	21.8	56.0	12.9	62.3	31.0	29.0
50	55.4	149.7	108.9	22.1	56.0	13.1	62.3	31.0	29.8
60	56.5	149.7	108.9	22.4	56.0	13.3	62.3	31.0	30.6
70	57.6	149.7	108.9	22.7	56.0	13.5	62.3	31.0	31.4

SUPPLEMENTAL TABLE S10-iii: ISCEV ERG: 90% CONFIDENCE INTERVAL OF: UPPER LMIT IMPLICIT TIME

Parameter	DA Red x-wave	DA Red b-wave	DA01	DA3 a-wave	DA3 b-wave	DA10 a-wave	DA10 b-wave	LA3	30 Hz
20	50 - 54	140 - 161	104 - 114	20.7 - 21.6	54 - 58	12.0 - 13.1	59 - 66	30.3 - 31.8	26.5 - 28.6
30	51 - 55	140 - 161	104 - 114	21.0 - 21.9	54 - 58	12.2 - 13.3	59 - 66	30.3 - 31.8	27.2 - 29.3
40	52 - 57	140 - 161	104 - 114	21.3 - 22.2	54 - 58	12.3 - 13.5	59 - 66	30.3 - 31.8	27.9 - 30.1
50	53 - 58	140 - 161	104 - 114	21.6 - 22.5	54 - 58	12.5 - 13.7	59 - 66	30.3 - 31.8	28.7 - 30.9
60	54 - 59	140 - 161	104 - 114	21.9 - 22.8	54 - 58	12.7 - 13.9	59 - 66	30.3 - 31.8	29.5 - 31.8
70	55 - 60	140 - 161	104 - 114	22.3 - 23.2	54 - 58	12.9 - 14.1	59 - 66	30.3 - 31.8	30.3 - 32.6

† = no correlation with age

Supplemental Reference Table S11: Summary of ISCEV Standard ffERG Amplitudes

Reference	N	Age (y) Mean ± SD [Range]	Filter (Hz)	DA01	DA3 a-wave	DA3 b-wave	LA3	30Hz
Current*	40	39.4 ± 15.7 [20-74]	0.1 - 329	**286 [161] †**	**275 [172] †**	**489 [328] †**	**185 [100] †**	***145 [65] ‡***
Weleber 1981[1]§	24	[9 – 67]	0.1 - 1000	**349 †**	NR	**574 †**	**149 †**	NR
Birch 1992[2]││	269	[5 – 79]	2.0 - 300	**135 [92] †**	NR	**331 [235] †**	**91 [60] †**	NR
Fulton 2003[3]# • Boston** • Toronto	35 68	22 [20-52] 30 [20-40]	1.0 - 1000 0.3 - 1000	253 231	184 274	425 543	137 164	NR NR
Beeler 2007[4]††	36	NR	NR	**314 †**	**240 †**	**538 †**	***148 ‡***	***103 ‡***
Studies using DTL electrodes for comparison								
Pravesh 2009[5]	180	[1-80]	NR	**128/132**	**198/201**	**408/407**	***156/157***	***99/97***
Jung 2024[6]	73	41 ± 17 [14-73]	NR	**313 †**	**258 †**	**437 †**	***184 ‡***	***130 ‡***

* = mean given for 40 y; **bolded**: tested for correlations with age**;** † = significant correlation with age; ‡ = not correlated with age; § Mean given for 40 y for Intensities chosen closest to ISCEV standard (White +ND2.4, White Grass setting 16 with ND2.4 (DA01) and ND0.2 (DA3/LA3), ││ = mean given for 35-44y, intensity for dim flash (DA01) was 100< than ISCEV standard ;

§ = median age and median amplitudes; ** = chromatic flashes, blue (Wratten 47B) for scotopic ERG, red (Wratten 29) for photopic ERG.

†† mean for 40-60 y with Henke's monopolar contact lens electrode

Supplemental Reference Table S12: Summary of ISCEV Standard ffERG Implicit Times

Paper	N	Age (y) Mean ± SD [Range]	Filter (Hz)	DA01	DA3 a-wave	DA3 b-wave	LA3	30Hz
Current*	40	39.4 ± 15.7 [20-74]	0.1- 329	***93.5 ‡***	**20.3 †**	***49.5 ‡***	***28.4 ‡***	**25.3 †**
Weleber 1981[1]§	24	[9 – 67]	0.1 - 1000	**80 ‡**	NR	***50.2 ‡***	***26.8‡***	NR
Birch 1992[2]❘❘	269	[5 – 79]	2.0 - 300	**81.3 †**	NR	**37.2 †**	**28.2 †**	**24.7 †** (derived)
Fulton 2003[3]# • Boston** • Toronto	 35 68	 22 [20-52] 30 [20-40]	 1.0 - 1000 0.3 - 1000	 79 114	 18 20	 46 45	 28 29	 NR NR
Beeler 2007[4]††	36	NR	NR	NR	NR	NR	**28.9 ‡**	**26.5 ‡**
Studies using DTL electrodes for comparison								
Pravesh 2009 [5]	180	[1-80]	NR	92/92	24/24	44/44	**31/31**	**27/26**
Jung 2024 [6]	73	41 ± 17 [14-73]	NR	**85 †**	**15 †**	***49 ‡***	***28 ‡***	***18 ‡***

* = mean given for 40 y; **bolded**: tested for correlations with age**;** † = significant correlation with age; ‡ = not correlated with age; § Mean given for 40 y for Intensities chosen closest to ISCEV standard (White +ND2.4, White Grass setting 16 with ND2.4 (DA01) and ND0.2 (DA3/LA3), ❘❘ = mean given for 35-44y, intensity for dim flash (DA01) was 100< than ISCEV standard ; § = median age and median implicit times; ** = chromatic flashes, blue (Wratten 47B) for scotopic ERG, red (Wratten 29) for photopic ERG. †† mean for 40-60 y with Henke's monopolar contact lens electrode

Abbreviations: y = years; Hz – hertz; NR = not reported.

Supplemental Reference Table S13: Summary of ISCEV Extended Protocol: Dark-Adapted Red Flash

Paper	Electrode	N	Age (y) Mean ± SD [Range]	Filter (Hz)	Stimulus λ (nm) / strength (cd-s/m²)	X-wave amplitude (µV)	b-wave amplitude (µV)	Ratio x-wave/ b-wave	x-wave IT (ms)	b-wave IT (ms)
ISCEV Standard [7]	NA				635-650/0.3	N/A				
Current*	RM	32	39.4 ± 15.7 [20-74]	0.1- 329	655/0.28	**129 ‡**	**141 †**	**0.34 ‡**	**47.9 †**	**119.7 ‡**
Weleber 1981 [1]	BA	17	[9-67]	0.1-1000	605 (KW26)+ND0.2/ max = 4.4 cd-s/m² prior to filter	**157 ‡**	**288 †**	NR	**48.2 ‡**	**102 ‡**
Lim 2005 [8]	BA	52 (88 eyes)	28.9 ± 8.36 [10-48]	0.3-500	605 (KW26)/ max = 2.4 cd-s/m² prior to filter	**172 ‡**	**214 ‡**	NR	**46 ‡**	**76.3 ‡**

* = mean given for 40 y; **bolded**: tested for correlations with age; † = significant correlation with age; ‡ = not correlated with age

Abbreviations: λ = wavelength; cd-s/m² = candela-sec/meter squared; Hz = hertz; IT = implicit time; KW26 = Kodak Wratten #26 filter; ms = millisecond; N = number of participants; N/A = not applicable; ND = neutral density; nm = nanometers; NR = not reported; SD = standard deviation; µV = microvolts; y = years.

Supplemental Reference Table S14: ISCEV Extended Protocol: Photopic Negative Response (PhNR): Red on Blue

Reference	Electrode	N	Age (y) Mean ± SD [Range]	Filter (Hz)	Stimulus λ (nm) /strength (cd-s/m²)	Background λ (nm) / strength (cd/m²)	BT amplitude (µV)	PT amplitude (µV)	Ratio PhNR/ b-wave	PhNR IT (ms)
ISCEV extended protocol[9]	N/A			≤0.3 - ≥300	630-660/ 1.0-2.5	450-485/ 10	N/A			
Current*	RM	32	39.4 ± 15.7 [20-74]	0.1- 329	655/1.4	455/8.0	***33 ‡***	***119 ‡***	***0.31 ‡***	**64.6 †**
Chen 2008[10]	CL§	43	57 ± 9.6 [40-74]	NR	635/5	465/10	78	NR	NR	71.5
Kremers [11]**	JET	14	41 ± 8.6	0.5-300	635/	476/10	58	NR	NR	75
Non-contact lens electrode Studies for comparison										
Sustar2009[12]	H-K loop	20	25.6 [19-35]	0.1-500	635/2.5	470/10	25	NR	0.34||	NR
Mortlock 2010[13]	DTL	31	[21-40]	1-1000	>625/1.5	450/20 (derived)	25	66	0.40||	69.8
Tang 2014[14]	DTL	49	38.9 [21-72]	0.15-100	635/1	465/10	***16 ‡***	***81 ‡***	0.2||	NR
Joshi 2017[15]	DTL	45	49# [24-74]	0-300	660/<=1.6	485/7	***28 ‡***	***80 ‡***	0.35||	NR
Studies using White stimuli and/or background										
Miyata 2007[16]	BA	25	[24-55]	0.1-500	White/1.9	White/18	34 ± 9	NR	0.4	NR
Sustar2009[12]	H-K loop	20	25.6 [19-35]	0.1-500	White/2.5	470/10	20 ± 6	NR	NR	0.23

* = mean given for 40 y; **bolded**: tested for correlations with age; † = significant correlation with age; ‡ = not correlated with age; § type of contract lens electrode not specified; | |= derived result from reported means of BT and b-wave amplitudes: ie. not reported as means of individuals; # = median age; **values derived from figures

Abbreviations: λ = wavelength; BT: baseline to trough; cd-s/m² = candela-sec/meter squared; CL = contact lens electrode; Hz = hertz; IT = implicit time; ms = millisecond; N = number of participants; N/A = not applicable; nm = nanometers; NR = not reported, PhNR = photopic negative response; PT = b-wave peak to trough; SD = standard deviation; µV = microvolts; y = years;

Supplemental Reference Table S15: ISCEV Extended Protocol: Photopic Negative Response (PhNR): Blue on Yellow

Reference	Electrode	N	Age (y) Mean ± SD [Range]	Filter (Hz)	Stimulus λ (nm) /strength (cd-s/m²)	Background λ (nm) / strength (cd-s/m²)	BT amplitude (µV)	PT amplitude (µV)	Ratio PhNR/ b-wave	PhNR IT (ms)
Current*	RM	32	39.4 ± 15.7 [20-74]	0.1- 329	455/0.09	591/10.1	**64 ‡**	**124 ‡**	**0.78 ‡**	**106.2 ‡**
Chen 2008[10]	JET	14	41.5 ± 18.6	0.5-300	458/0.03-3.0	591/10.0	77	NR	NR	100

Supplemental Reference Table S16: Summary of ISCEV Extended Protocol: Photopic ON-OFF

Paper	Electrode	N	Age (y) Mean ± SD [Range]	Filter (Hz)	Stimulus strength (cd/m²)	Background intensity (cd/m²)	Onset Duration (ms)	b-wave amplitude (µV)	d-wave amplitude (µV)	b-wave IT (ms)	d-wave IT (ms)
ISCEV Standard[17]	N/A				250 [150-350]	30	150-200	NA			
Current*	RM	36	39.4 ± 15.7 [20-74]	0.1-329	252	28	150	***75 ‡***	***55 ‡***	**33.2 †**	**21.9 †**
Sieving 1993[18]	BA	46	NR	1-1000	185	43	150	48	35	NR	NR
Yamamoto 2002§[19]	CL (mono)	12	[6-45]	NR	300	40	200	25-79	22-61	30.4-36	20-23
Hota 2006[20]	CL (mono)	8	56 ± 10 [45-70]	NR	360	40	100	61	74	33.1	21.1
Moskowitz 2012‖[21]	BA	61	26 [8-60]	NR	200	40	150	48	35	35.5	22
Non-contact lens electrode Studies for comparison											
Allen 2003[22]	Gold foil	15	NR	NR	398	48	200	67	49	NR	NR
Sustar 2008[23]	HK loop	10	24 [9-32]	0.1-1000	50	20	200	48	29	34	16
Constable 2016[24]	DTL	10	35.3 ± 12.9 [14-58]	NR	133	43	120	49	28	34	20
Jung 2024[6]	DTL	73	41 ± 17 [14-73]	NR	80	20	240	**51 ‡**	**31 ‡**	**30 †**	**19 †**

* = mean given for 40 y; **bolded**: tested for correlations with age; † = significant correlation with age; ‡ = not correlated with age; § = only reported 95% confidence intervals; || = median age;

Abbreviations: cd/m² = candela/meter squared; CL = contact lens electrode; Hz = hertz; IT = implicit time; mono = monocular; ms = millisecond; N= number of participants; N/A = not applicable; nm = nanometers; NR = not reported; SD = standard deviation; µV = microvolts; y = years;

Supplemental Reference Table S17: Summary of ISCEV Extended Protocol: S-cone

Reference	Electrode	N	Age (y) Mean ± SD [Range]	Filter (Hz)	Stimulus λ (nm) / strength (cd-s/m^2)	Background λ (nm) /strength (cd-s/m^2)	s-cone amplitude (µV)	s-cone IT (ms)
ISCEV Standard[25]	N/A			≤0.3 - ≥300	450-470/ 0.05 [0.025-0.2] Or [0.1-0.5]	570-620/ 300 OR [500-600]	N/A	
Current*	RM	26	39.4 ± 15.7 [20-74]	0.1- 329	455/0.05	591/321	***5.9 ‡***	***38.5 ‡***
Simonsen 1996[26]	BA (mono)	33	Median = 34 [13-58]	NR	440 (KW 98) max = 2.4 cd-s/m^2 prior to filter	>530 nm (SG OG530)/100	**5.0 †**	41.5
Marmor 2004[27]	BA	32	[19-49]	NR	440/0.03-0.05	590/300	3-9	45-53
Non-contact lens electrode Studies for comparison								
Chiti 2003[28]	DTL	24 73	[20-30] [20-80]	1-100	430 nm (Lee Filter 071) +450nm Schott BG28)/ 0.034	>585 nm/215	3.95	42.5
Wakili 2008[29]	DTL	37	53 ± 13.6	1-100	440 (KW 47) 0.013-**0.052**)	550 (KW 12)/238	3.3	47.5
Sustar 2011[30]	H-K loop	20	[18-35]	0.1-500	449 (KW 47B) 0.032-0.063	594/100	3.9	42.1
Schatz 2014§[31]	DTL	12	35.5 ± 9.4 [25-54]	0.03-30	470/0.1-0.5	594/500	13.2	40.7
Campi 2017[32]	DTL	31	34 ± 8.8 [20-49]	0.1-100	445/0.4	600/560	5.6	NR
Jung 2024[6]	DTL	73	41 ± 17 [14-73]	NR	470/0.2	590/300	***6 ‡***	***46 ‡***

* = mean given for 40 y; **bolded**: tested for correlations with age † = implied correlation with age but no stats provided**;** ‡ = not correlated with age; § Filtered <30 Hz to remove L/M and measured from preceding trough to peak of b-wave

Abbreviations: λ = wavelength; cd-s/m^2 = candela-sec/meter squared; Hz = hertz; IT = implicit time; KW 98 = Kodak Wratten filter; ms = millisecond; N = number of participants; N/A = not applicable; nm = nanometers; NR = not reported; SD = standard deviation; µV = microvolts**;** y = years;

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