

Optimizing a Portable ERG Device for Glaucoma Clinic: The Effect of Interstimulus Frequency on the Photopic Negative Response

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Purpose: The purpose of this study was to investigate the effect of interstimulus frequency on the photopic negative response (PhNR) in the clinical electroretinogram (ERG) in glaucoma and healthy eyes.

Methods: Participants with open angle glaucoma ($n = 15$) and age-matched controls ($n = 20$) were recruited. Photopic ERGs were recorded in one eye using five frequencies (1–5 Hz) delivered in random order. ERGs were analyzed for changes to amplitude and timing between groups and interstimulus frequency. Coefficient of variation (CoV) was used to examine variability within recordings for each frequency.

Results: While the a-wave and b-wave showed minimal alteration, the PhNR was highly sensitive to changes in interstimulus frequency. The PhNR signal was largest at 1 Hz and steadily diminished with higher frequencies in both control and glaucoma groups. Significant differences in PhNR amplitude were found between controls and glaucoma groups at 2 and 3 Hz. While 1 Hz delivered the largest PhNR, it also showed a significantly greater CoV compared to other frequencies.

Conclusions: An interstimulus frequency of 2 Hz was optimal for recording the PhNR, creating a good balance between testing time and signal quality. A higher frequency could be used to further shorten clinical testing times; however, this may compromise its clinical utility by dampening the PhNR.

Translational Relevance: Here we show the importance of considering flash interstimulus frequency when designing ERG protocols for recording the PhNR as while higher frequencies can shorten test times, they also have considerable effects on the PhNR.

Introduction

Clinical electroretinograms (ERGs) are gaining more widespread attention due to the introduction of handheld recording devices, the use of which has broadened the possibility of using ERG as a screening tool and for longitudinal patient monitoring. This includes using the photopic negative response (PhNR) of the light-adapted ERG, which may be useful as an objective marker of retinal ganglion cell (RGC) function in glaucoma.¹ Previous studies have shown that the PhNR is reduced in eyes with glaucoma, similar to the pattern electroretinogram (PERG).^{2,3}

There is some advantage in recording the PhNR compared to other electrophysiological measures such as the PERG and scotopic threshold response in the clinic as it is more robust to cataract, does not require refractive correction, and does not require dark adaptation, thus increasing its potential for clinical translation.^{4,5} This is of particular interest in glaucoma management, where the PhNR may provide additional objective information on RGC function and may be utilized as an alternative for people who do not perform well on perimetry. Objective measures of RGC function in glaucoma would be attractive if

Table 1. An Example of the Variation in Clinical Protocols for Measuring the PhNR Across the Literature

Literature	Blue Background	Red Flash	Interstimulus Frequency, Hz
Binns et al. ⁷	3.9 log scot td.s	0.05–3.39 cd.s/m ²	4
Chen et al. ⁸	10 cd/m ²	1, 5, 7 cd.s/m ²	NR
Chen et al. ⁹	10 cd/m ²	5 cd.s/m ²	NR
Cvenkel et al. ³	10 cd/m ²	2.5 cd.s/m ²	1
Gotoh et al. ¹⁰	40 cd/m ² (white)	3 log cd/m ²	0.5
Horn et al. ¹¹	20 cd/m ² (white)	40, 60, 80 cd.s/m ²	2
Huang et al. ¹²	25 cd/m ² (white)	2.00 cd.s/m ²	<0.5
Joshi et al. ¹³	7 phot cd/m ²	0.00625–1.6 cd.s/m ²	1
Kim et al. ¹⁴	30 cd/m ² (white)	2.4297 cd.s/m ²	<0.5
Kirkiewicz et al. ¹⁵	25 cd/m ²	1.6 cd.s/m ²	NR
Kremers et al. ¹⁶	10 cd/m ²	0.03, 0.1, 1, 3 cd.s/m ²	1
Machida et al. ^{17,18}	40 cd/m ²	4.8 cd.s/m ²	1
Mortlock et al. ¹⁹	3.9 log scot td	1.5 cd.s/m ²	4
Niyadurupola et al. ²⁰	20 cd/m ²	2.25, 3 cd.s/m ²	NR
Preiser et al. ²	10 cd/m ²	0.1–4 cd.s/m ²	1
Rangaswamy et al. ²¹	100 scot cd/m ²	0.04–2.84 cd.s/m ²	NR
Shen et al. ²²	25 cd/m ²	2 cd.s/m ²	0.5
Sustar et al. ²³	10 phot cd/m ²	0.08–7.5 cd.s/m ²	1
Tang et al. ²⁴	10 cd/m ²	0.5, 1, 2.25, 3 cd.s/m ²	1
Viswanathan et al. ²⁵	3.7 log scot td	0.5–2.0 log phot td.s	NR
Wang et al. ²⁶	100 scot cd/m ²	0.04–2.84 cd.s/m ²	NR
Wu et al. ²⁷	10 cd/m ²	58 td.s	3.43

NR, not reported.

such measures were clinically feasible, with demonstrated good utility.

The PhNR can be a noisy signal and usually requires multiple repeated flash stimuli to improve the signal-to-noise ratio (with protocols ranging from 10 to 200 sweeps) for each stimulus intensity and an average taken. This makes the interstimulus frequency (the rate of flash delivery) an important aspect to consider when designing clinical protocols because increasing the frequency would reduce testing times, making it more tolerable for patients, and would assist its uptake into clinical practice. A wide range of recording protocols have been utilized across the literature, with varying stimulus intensity, number of sweeps, and interstimulus frequency (Table 1). The International Society for Clinical Electrophysiology of Vision (ISCEV) have recently released a set of guidelines surrounding the recording of the PhNR in the clinic,⁶ with a recommended interstimulus frequency of 1 Hz. However, there are yet to be any systematic studies on the influence of altering interstimulus frequency on the PhNR. Here we explore the effect of a range of frequencies on the ERG in healthy adults and glaucoma participants.

Methods

All procedures adhered to the tenets of the Declaration of Helsinki and were approved by the Human Research Ethics Committee at the Royal Victorian Eye and Ear Hospital (13/1121H). Informed consent was obtained from all participants prior to all procedures.

Participants ($n = 20$ controls, $n = 15$ glaucoma) were recruited from the glaucoma and surgical outpatient clinics at the Royal Victorian Eye and Ear Hospital. Participants with early open angle glaucoma were recruited. Each participant was diagnosed by a glaucoma specialist, demonstrated reproducible visual field defects on a field analyzer (Humphrey 24-2 SITA Threshold; Carl Zeiss Meditec AG, Jena, Germany) of at least three neighboring points on the total deviation plot with a probability of <2%.²⁸ Early glaucoma was classified by visual field mean deviation (MD) of better than 6 dB. Control participants were recruited from surgical outpatient clinics at the hospital and underwent a full slit lamp eye examination prior to testing. Intraocular pressure

(IOP) was measured via Goldmann applanation tonometry. All participants had an IOP ≤ 21 mm Hg with or without treatment at the time of study participation. Exclusion criteria included visual acuity $< 6/18$; diabetes and/or diabetic retinopathy; other ocular diseases, including age-related macular degeneration; uveitis; and previous intraocular surgery in the last 6 months (uncomplicated cataract surgery within the last 3 months). The same criteria were applied to control participants. Where both eyes were eligible for the study, one eye was chosen at random for testing.

Photopic ERGs were recorded in one eye per participant with a handheld device (RETeval; LKC Technologies, Gaithersburg, MD) using a series of red flashes (621 nm, 1 cd.s/m²) on a blue background (470 nm, 10 photopic cd/m²). Stimuli were calibrated using a radiometer (ILT-1700; International Light Technologies, Newburyport, MA) with photopic filter in place. Participants were light-adapted for at least 10 minutes in the clinical testing room prior to testing. Pupils were dilated (to ≥ 6 mm) using 0.5% tropicamide (Mydracyl; Alcon Laboratories, Macquarie Park, NSW, Australia) and 2.5% phenylephrine (Bausch and Lomb, Chatswood, NSW, Australia). Custom-made DTL-like electrodes using silver impregnated fiber (22/1 dtex; Shieldex Trading, Palmyra, NY) were used for all recordings. Reference and ground gold-cup electrodes (Grass Technologies; Astro-Med Inc., West Warwick, RI) were placed at the temple and forehead, respectively. A series of interstimulus frequencies were tested (between 1 and 5 Hz in 1-Hz steps, 100 sweeps per frequency). Five hertz was chosen as the highest frequency tested, which is a step higher than what has been previously used in literature (Table 1).^{7,19} The lower limit was set at 1 Hz, in accordance to ISCEV guidelines and to prevent long recording times. The order of frequencies tested was randomized, and participants were given at least 1 minute break between each change of frequency.

Raw traces were extracted offline and processed using custom-written Matlab scripts (R2017a; MathWorks, Natick, MA). A bandpass filter (0.3–300 Hz) was applied to the raw data. Traces were detrended with a third-order polynomial fitted to the entire signal because, as we have shown previously, this method provided the most robust PhNR signal with greatest repeatability while retaining its diagnostic ability in glaucoma.²⁹ From this, the amplitudes of the a-wave, b-wave (measured from a-wave trough to b-wave peak), and PhNR were extracted, as well as

their respective implicit times. The PhNR amplitude was measured in three ways: (1) as a minimum from the baseline to trough (BT), (2) from the b-wave peak to PhNR trough (PT), and (3) as a ratio to the b-wave (ratio).

To investigate changes associated with interstimulus frequency and the ERG, repeated measures (RM) 2-way ANOVA was used to compare controls to glaucoma, with frequency nested within. Tukey's multiple comparisons procedure was used where significance between groups was found. The area under receiver-operator characteristic (AUC) curves was calculated to examine the discriminative ability at each stimulus frequency. The coefficient of variation (CoV, standard deviation/mean) was determined for each ERG component to examine the differences in recording variability for each frequency. Data, unless stated otherwise, are shown as mean \pm SEM.

Results

Age-matched control (mean \pm SD, 63 \pm 16 years) and glaucoma participants (71 \pm 13 years) were recruited. Participants with early glaucoma were recruited (average MD: -4.4 ± 1.4 dB). Control participants demonstrated no ocular pathology aside from visually insignificant, age-normal cataracts. There was no significant difference in IOP between groups (control: 13.1 \pm 1.1 mm Hg, glaucoma: 13.9 \pm 1.0 mm Hg; Student's *t*-test, $P = 0.46$).

Figure 1 shows the group average ERG waveforms from 1 Hz (navy blue) to 5 Hz (maroon red) in the control and glaucoma groups. As interstimulus frequency increased, mild changes can be qualitatively observed to the a-wave and b-wave. However, the PhNR demonstrates a marked reduction in amplitude with increasing frequency in both cohorts. All average ERG traces showed return to baseline for all frequencies (not shown).

Figure 2 shows the a-wave and b-wave amplitude and timing in healthy and glaucoma groups with changing frequency. While small disparities in amplitude and timing can be observed with frequency, there were no significant differences for the a-wave (amplitude: $F_{4,132} = 1.74$, $P = 0.15$; implicit time: $F_{4,132} = 0.58$, $P = 0.68$) and b-wave (amplitude: $F_{4,132} = 1.65$, $P = 0.17$; implicit time: $F_{4,132} = 0.56$, $P = 0.70$). In addition, no statistically significant differences were obtained between control and glaucoma groups.

While the outer retinal responses remained largely unaltered, the PhNR showed impressive changes with interstimulus frequency (Fig. 3). With every method

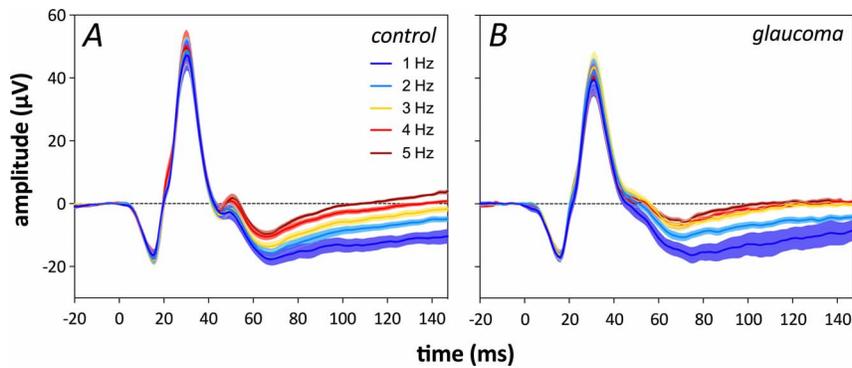


Figure 1. Group average ERG traces for control (A) and glaucoma (B) participants for each interstimulus frequency (1–5 Hz, blue to red). The time is truncated here to highlight the PT changes.

used to measure the PhNR, the amplitude steadily reduced with increasing frequency in both groups ($P < 0.0001$; **Figure 3A–C**). The glaucoma group also demonstrated greater attenuation of the PhNR BT compared to controls ($F_{1,33} = 4.84$, $P = 0.03$). This was most apparent at 2 and 3 Hz on post hoc testing. A reduction in amplitude was also coupled with a faster PhNR implicit time in both control and glaucoma groups ($P < 0.0001$; **Fig. 3D**) with increasing frequency.

From this, it is apparent that a significant drop-off in the PhNR signal is seen as the interstimulus frequency is elevated above 1 Hz. However, the PhNR amplitude measured at 1 Hz could not

differentiate between disease groups compared to higher interstimulus frequencies and showed poor diagnostic ability (**Table 2**). Indeed, the 1-Hz ERG traces tended to demonstrate increased variability within each averaged trace compared to other interstimulus frequencies (**Supplementary Fig. S1** shows a representative ERG trace of 1 and 2 Hz). **Figure 4** highlights the significantly larger CoV in the 1-Hz ERG traces compared to other interstimulus frequencies. The 1-Hz CoV was greatest for the a-wave, followed by the PhNR and b-wave, whereas all other frequencies (2, 3, 4, and 5 Hz) had significantly reduced CoV compared to 1 Hz.

Increasing interstimulus frequency from 1 to 2 Hz

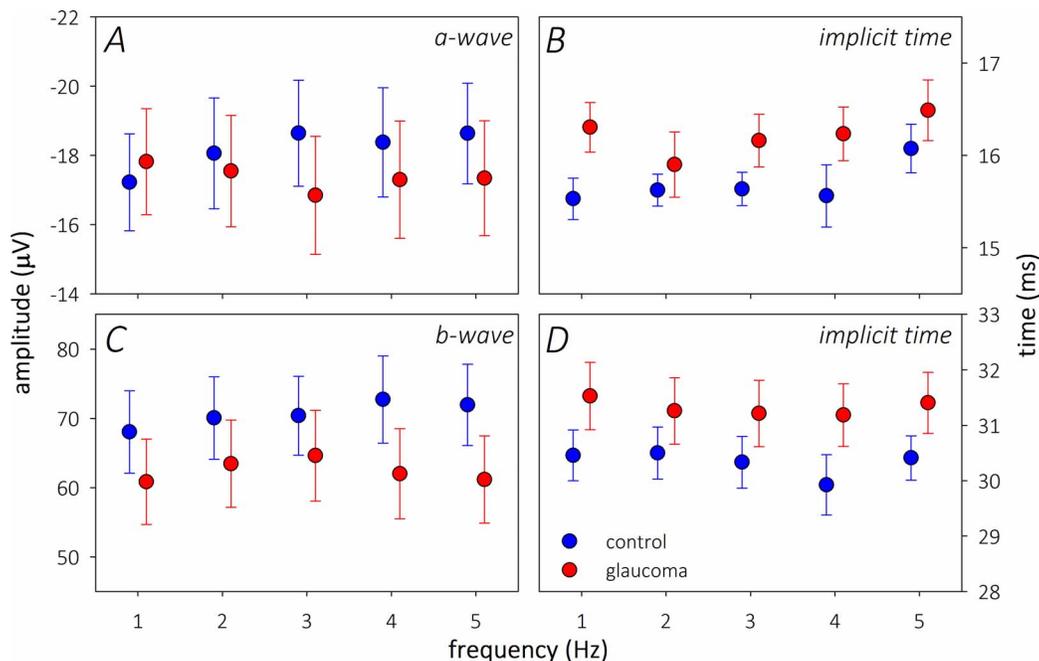


Figure 2. The a-wave amplitude and implicit time (A, B) and b-wave amplitude and implicit time (C, D), with increasing interstimulus frequency in control (blue) and glaucoma (red) groups.

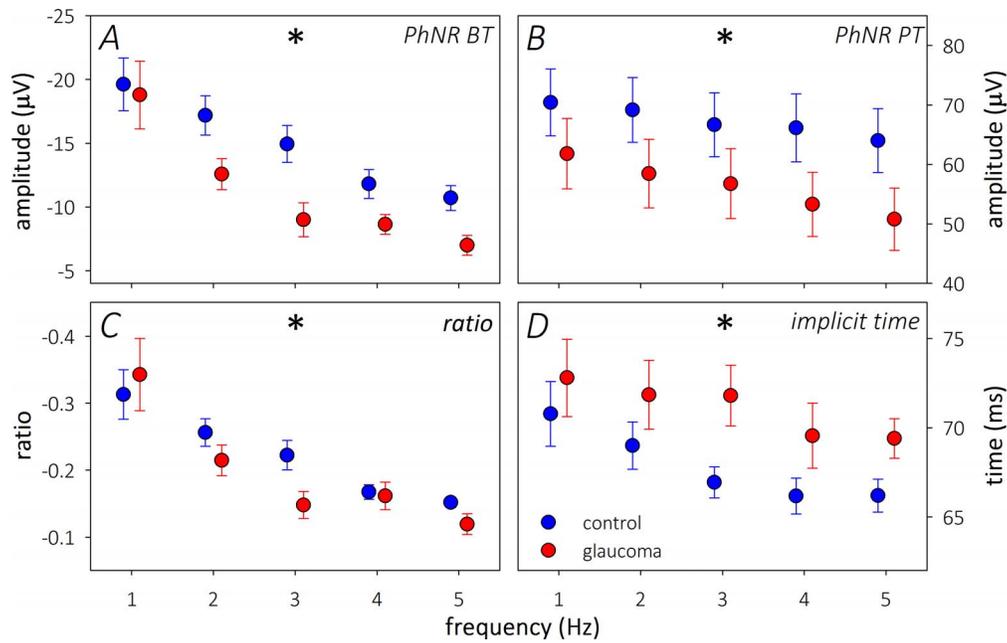


Figure 3. Changes to the PhNR amplitude: (A) BT, (B) b-wave PT, (C) BT/b-wave ratio, and implicit time (D) for control (blue) and glaucoma (red) groups in response to increasing interstimulus frequency. *Significance on 2-way RM-ANOVA with changing frequency.

reduced CoV considerably for the a-wave and PhNR in both control and glaucoma groups. However, there was no further reduction in CoV when increasing the interstimulus frequency above 2 Hz. While using an interstimulus frequency above 2 Hz would shorten testing times further, Figure 5 shows that it also causes a significant dampening of the PhNR BT (Fig. 5A) compared to 2 Hz, with a $-27.4\% \pm 16.9\%$ (mean \pm 95% confidence interval [CI]) reduction at 3 Hz, to $-33.7\% \pm 8.9\%$ at 5 Hz. The ratio was similarly affected (Fig. 5C). Therefore, while 3 and 5 Hz also demonstrated good diagnostic ability (Table 2), the amplitude reduction seen with

these higher interstimulus frequencies may limit its clinical utility for potential longitudinal monitoring in glaucoma.

Discussion

To our knowledge, this is the first systematic study on the effect of interstimulus frequency on the PhNR in healthy and glaucoma eyes. There have been large variations in clinical protocols utilized in the past, but for ERG recording to gain traction in the clinic for patient monitoring, there must be a balance between the length of clinical test times and quality of ERG recordings. One way of shortening test times is by increasing the interstimulus frequency, whereby a greater number of flashes are delivered per second. We found that while test times could be reduced, this came at a cost of significantly reducing the PhNR (Fig. 3). While some diagnostic ability may be retained with higher interstimulus frequencies, a smaller PhNR signal may affect its utility in detecting longitudinal changes over time.

Currently, ISCEV recommends an interstimulus frequency of 2 Hz for photopic (white on white) ERG recordings to minimize potential changes to the a- and b-wave.³⁰ It is interesting that we found the a- and b-wave to be robust to alterations in frequency in both control and glaucoma groups. This may be explained

Table 2. AUC Showing the Differences in Discriminative Ability Between Interstimulus Frequencies Tested

Interstimulus Frequency, Hz	AUC	95% CI	P Value
1	0.56	0.36 to 0.75	0.57
2	0.72	0.55 to 0.89	0.03*
3	0.78	0.63 to 0.94	0.005*
4	0.68	0.50 to 0.86	0.08
5	0.76	0.60 to 0.92	0.01*

CI, confidence interval.
* Denotes significance.

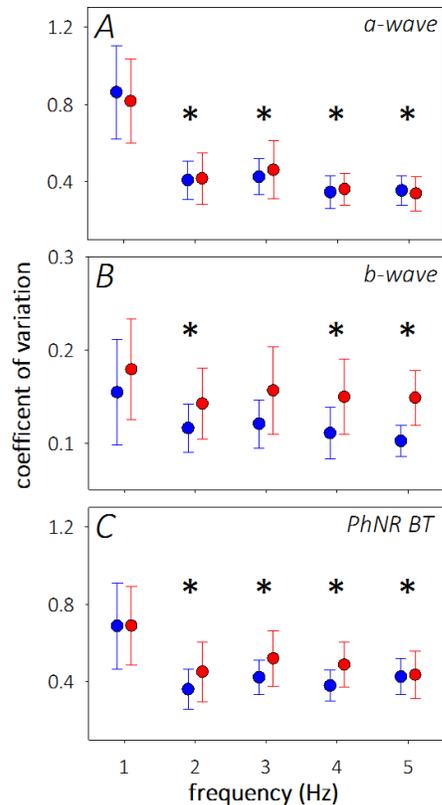


Figure 4. CoV of the a-wave (A), b-wave (B), and PhNR (C) amplitudes measured at the implicit time for control (blue) and glaucoma (red) groups. Two-way ANOVA with Tukey's multiple comparisons. *Significance compared to 1 Hz; no differences were found between other stimulus frequencies.

by the different stimulus conditions utilized in this study, as we used a red-on-blue flash stimulus of a dimmer luminance (1 cd.s/m^2 as opposed to 3 cd.s/m^2). Current literature is inconclusive about whether the outer retina is affected in glaucoma.^{31–34} As this study was not designed to examine differences in the a- and b-wave in glaucoma, only a trend for a smaller outer retinal response in the glaucoma group was observed (Fig. 2). Future studies involving a series of stimulus intensities could be used to probe this question further.

The PhNR shows the most pronounced change with frequency, suggesting that there may be insufficient time for full retinal recovery when recording at the higher interstimulus frequencies. While all ERG traces in this study returned to baseline prior to the next flash, the PhNR demonstrated a much sharper and smaller trough with increasing frequency. A smaller PhNR when measured with a higher frequency has been alluded

to in the past when Binns et al.⁷ compared interstimulus frequencies of 0.5 and 4 Hz. Although the PhNR appeared to be slightly reduced at 4 Hz, this was only shown for a single individual. While 1 Hz has been recently recommended by ISCEV to measure the PhNR, we found it demonstrated the largest CoV within the average trace. This means that individual sweeps were more variable, which is likely to explain the greater group variability seen at 1 Hz (Fig. 3A) and the poor diagnostic ability compared to other interstimulus frequencies tested in this study (Table 2). However, some prior studies utilizing 1 Hz have successfully discriminated between control and eyes with manifest glaucoma.^{2,17} Preiser et al.² had similar stimulus conditions to this study and found a modest AUC (0.779). This was partly driven by the larger PhNR seen in their control group compared to ours, whereas similar amplitudes were seen in the glaucoma groups. Machida et al.¹⁷ also found significant differences between control and glaucoma groups, although a significantly brighter stimulus was utilized in their study (4.8 cd.s/m^2).

The greater variation we observed between sweeps at 1 Hz may mean longer recording times for ERG devices that allow manual rejection of sweeps, such as the Espion system, or that a larger number of sweeps are required to achieve an adequate signal in devices that do not have manual rejection, such as the RETeval. Therefore, although the PhNR amplitude was the largest at 1 Hz, it came at the cost of a significantly more variable signal. This can be ameliorated by utilizing a higher interstimulus frequency (2–5 Hz; Fig. 4C), with the additional benefit of shortening clinical test times. However, there was no additional improvement in CoV by increasing the interstimulus frequency beyond 2 Hz. While diagnostic ability could be retained at 3 and 5 Hz (Table 2), it comes coupled with a large reduction in PhNR amplitude seen beyond 2 Hz (Fig. 5), which may limit its clinical utility for longitudinal monitoring in glaucoma.

One of the precautions in using an interstimulus frequency of 1 Hz is to allow for full PhNR recovery. Here, we found that the ERGs recorded at all frequencies demonstrated a return to baseline before subsequent flashes. This can be partly due to the stimulus intensity used or potentially due to the dampened PhNR measured with higher interstimulus frequencies, which could allow for a more rapid return to baseline.

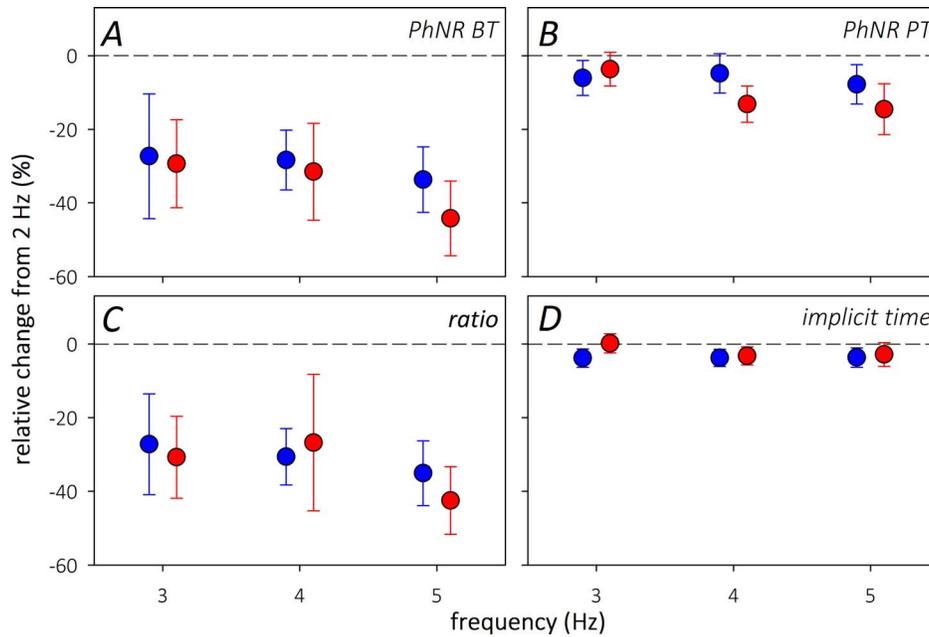


Figure 5. Changes to the PhNR BT (A), PT (B), ratio (C), and implicit time (D) expressed relative to the ERG measured at 2 Hz (%) for controls (blue) and glaucoma (red). Data expressed as mean \pm 95% CI. Dashed line indicates zero change.

Recommendations

Care must be taken when designing ERG protocols for recording the PhNR in the clinic. It is recommended to adhere to an interstimulus frequency of ≤ 2 Hz in healthy and glaucoma patients. At a frequency higher than that, the results should be interpreted carefully as there may be a reduction in PhNR amplitude or it may induce a change in timing that occurs irrespective of the patient's condition. Care should also be taken when comparing datasets of photopic ERG recordings that are measured with different interstimulus frequencies, given the effect it has on the PhNR.

Limitations

This is, to our knowledge, the first systematic study of the effect of interstimulus frequency on the PhNR. However, it was performed at one intensity of moderate luminance. There may be some differences if a brighter stimulus intensity were utilized, and this is worthy of future consideration. In this study, a single intensity was chosen to ensure that test times were kept manageable for participants. This intensity was chosen from the literature, which has shown that a good PhNR could be elicited at 1 cd.s/m² while maintaining good diagnostic ability in

glaucoma and is within the ISCEV recommendations.^{2,6,16}

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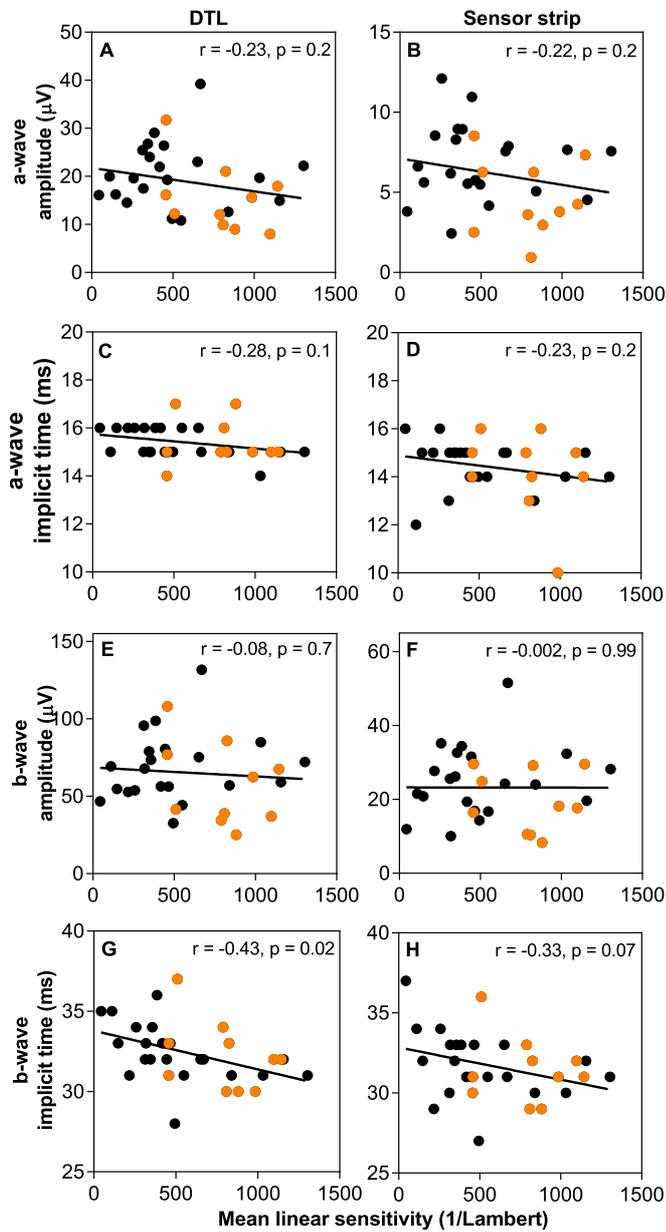


Figure S1: Correlation between mean light sensitivity and a-wave amplitude (A, B), a-wave implicit time (C, D), b-wave amplitude (E, F) and b-wave implicit time (G, H) for the DTL (left) and sensor strip (right) electrode in glaucoma (black circles) and glaucoma suspect (orange circles) participants.