Reversal Rate Dependence and Nasal-Temporal Field Differences in High Luminance Peripheral Pattern Electroretinogram (ppERG) Responses in Healthy Human eyes

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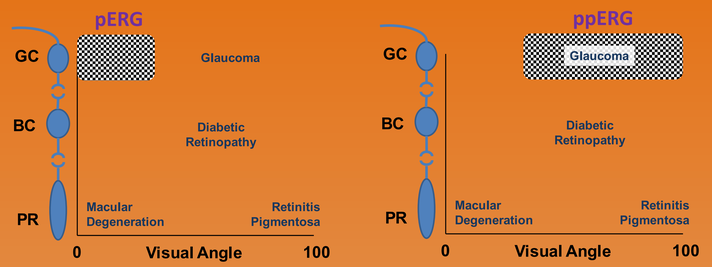
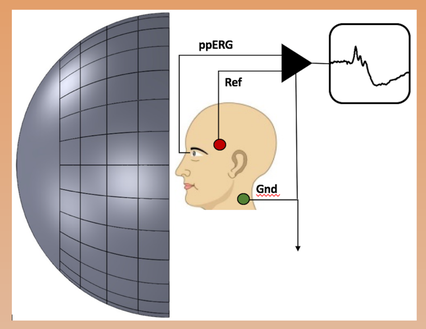
I. Introduction

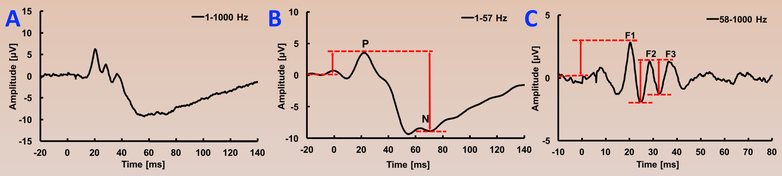


- Ganglion cell (GC) dysfunction due to glaucoma typically begins in the mid-periphery. The pattern ERG (**pERG**) evokes a response dominated by GC's, and is a sensitive measure of GC dysfunction associated with glaucoma.
- The conventional pERG stimulus subtends approximately ±15 degrees of visual angle. A pattern stimulus that probes the mid- and far-peripheral retina may be advantageous for detecting early stage glaucoma.
- The conventional pERG stimulus source is technology-limited to ~100 ph cd m^{-2}. A pattern stimulus source that delivers higher luminance may elicit larger amplitude responses, potentially decreasing test time to reach acceptable SNR.
- Here we recorded pattern ERG responses elicited from the mid- and far-peripheral retina, using a three-dimensional high-luminance stimulus source.
- These ***peripheral pattern ERG (ppERG)*** responses were characterized with respect to reversal rate and field subtended in healthy eyes. In addition, ppERG responses were compared to conventional pERG in a small group of glaucoma patients.

II. Methods



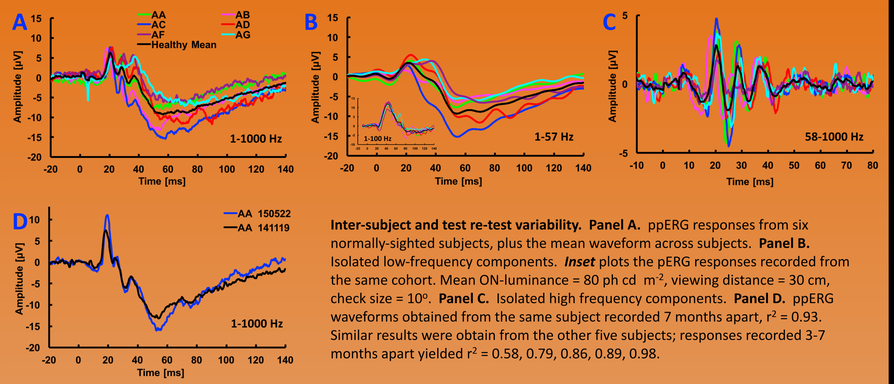
- A pattern stimulus was delivered to the peripheral retina via a hemispherical surface. Field subtended: 35° – 85° (half angle) in all directions. Unless otherwise stated, mean ON-luminance was 1670 photopic candelas per square meter (ph cd m^{-2}), reversal rate 4.6 reversals per second (RPS), check size 10°.
- Responses were recorded with DTL corneal electrodes; reference and ground on ipsilateral temple and neck, respectively.
- ppERG responses were amplified 10,000X, passband 1-1000 Hz, and digitized at 5 kHz. Responses were recorded in five-second epochs until at least 200 "clean" pattern reversals were recorded.



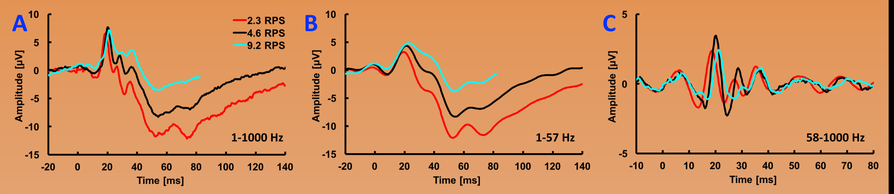
ppERG response waveform analysis. Waveforms were recorded from six normally-sighted subjects, and five glaucoma patients. **Panel A.** Typical ppERG response waveform (passband 1-1000 Hz) exhibits high- and low-frequency components; these were isolated prior to evaluation of each response for amplitudes and implicit times. **Panel B.** Isolated low-frequency components (1-57 Hz). Amplitude of the early positive component (**P**) was measured from baseline; amplitude of the late negative component (**N**) was measured from **P**. **Panel C.** Isolated high-frequency components (58-1000 Hz). **F1** was measured from baseline to peak; **F2** and **F3** are measured from the preceding trough to peak. For all components, peak and trough amplitudes were evaluated as the maximum or minimum values within standard time windows defined by the average response across the normally-sighted subjects.

Participants. Normally-sighted subjects had no history of eye disease, normal visual acuity, RNFL thickness within normal limits, and refractive error that ranged from 0 to -4.25 diopters. Patients with primary open-angle glaucoma had acuity better than 20/40, no media opacity, no prior glaucoma surgery, and HVF mean deviation ranged from -3.89 to -7.02.

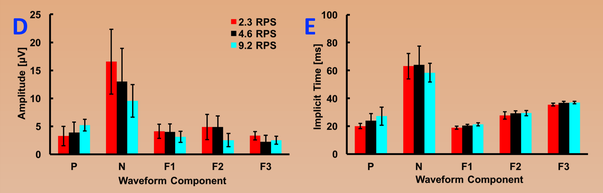
III. Results – Healthy Eyes



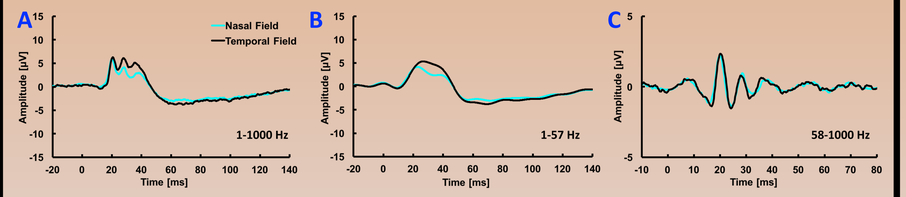
Inter-subject and test re-test variability. Panel A. ppERG responses from six normally-sighted subjects, plus the mean waveform across subjects. **Panel B.** Isolated low-frequency components. ***Inset*** plots the pERG responses recorded from the same cohort. Mean ON-luminance = 80 ph cd m^{-2}, viewing distance = 30 cm, check size = 10°. **Panel C.** Isolated high frequency components. **Panel D.** ppERG waveforms obtained from the same subject recorded 7 months apart, r^2 = 0.93. Similar results were obtain from the other five subjects; responses recorded 3-7 months apart yielded r^2 = 0.58, 0.79, 0.86, 0.89, 0.98.



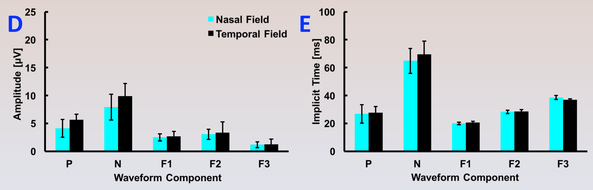
Dependence of ppERG responses on reversal rate. Panel A. Average transient ppERG response waveforms (n = 6) at 2.3, 4.6 and 9.2 reversals per second (RPS). **Panel B.** Isolated low frequency components. **Panel C.** Isolated high frequency components. **Panel D.** Amplitude of each response component (**P**, **N**, **F1**, **F2**, **F3**) at each reversal rate. **Panel E.** Implicit time of each response component at each reversal rate. Error bars in **D** and **E** plot ± one SD.



On average, with increasing reversal rate, amplitude of **P** increased (0.3 μV RMS^{-1}, r^2 = 0.27) and **N** decreased (-1.0 μV RMS^{-1} , r^2 = -0.23). The differences in amplitudes elicited with 2.3 and 9.6 RPS stimuli were significant for **P** (p = 0.02), and nearly so for **N** (p = 0.06). The high-frequency components were nearly constant for all reversal rates.

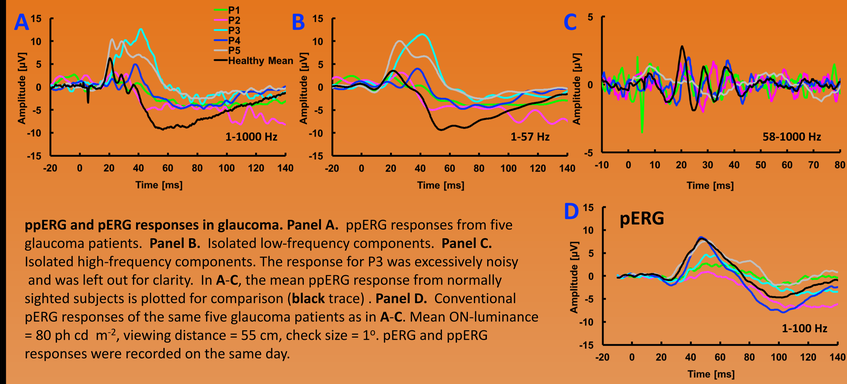


ppERG responses from nasal and temporal fields. Panel A. Average ppERG response waveforms (n = 6) elicited by a 4x4 check pattern presented to the nasal or temporal field. Stimulus pattern subtended 29°-70° of visual angle; this was achieved by moving the subject away from the stimulus source to a point where the inner edge of the pattern was no longer obstructed by the bridge of the nose. **Panel B.** Isolated low frequency components. **Panel C.** Isolated high-frequency components. **Panel D.** Amplitude of each response component (**P**, **N**, **F1**, **F2**, **F3**) evaluated for each field subtended. **Panel E.** Implicit time of each response component evaluated for each field subtended. Error bars in **D** and **E** plot ± one SD.

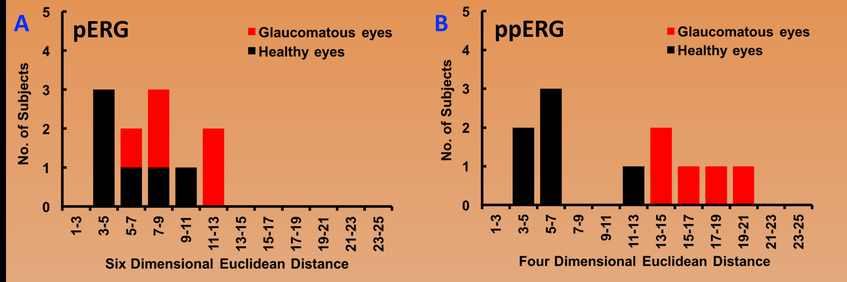


The mean amplitudes of both **P** and **N** were larger in the temporal field, but not significantly (p = 0.07, 0.17, respectively). The high-frequency component amplitudes were nearly constant in both fields. The difference in amplitudes may be due to the nasal-temporal asymmetry in ganglion cell density, which is greater in the nasal retina (temporal field).

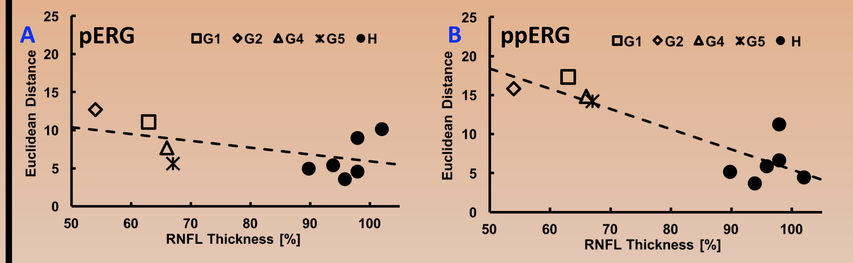
IV. Results – Glaucomatous Eyes



ppERG and pERG responses in glaucoma. Panel A. ppERG responses from five glaucoma patients. **Panel B.** Isolated low-frequency components. **Panel C.** Isolated high-frequency components. The response for P3 was excessively noisy and was left out for clarity. In **A**-**C**, the mean ppERG response from normally sighted subjects is plotted for comparison (**black** trace) . **Panel D.** Conventional pERG responses of the same five glaucoma patients as in **A**-**C**. Mean ON-luminance = 80 ph cd m^{-2}, viewing distance = 55 cm, check size = 1°. pERG and ppERG responses were recorded on the same day.



Cluster analysis comparing pERG and ppERG responses in glaucoma. Each subject (n = 6) and patient (n = 5) response was plotted in an ***n***-dimensional feature space, where ***n*** = 6 for pERG (amplitude and implicit time of **N35**, **P50**, **N95**), and ***n*** = 4 for ppERG (amplitude and implicit time of **P** and **N**). The distance of each patient / subject from the healthy-eye mean was calculated (leave-one-out cross validation for normally-sighted subjects). **Panel A.** Histogram plotting pERG results. **Panel B.** Histogram plotting ppERG results.



Correlation of functional test results with RNFL thickness. Euclidean distance from the healthy-eye mean in the feature space plotted against retinal nerve fiber layer (RNFL) thickness. RNFL was converted to percent of normal for each participant's age group. **Panel A.** Results for pERG, slope of best fit line = -0.09 $\%^{-1}$. **Panel B.** Results for ppERG, slope of best-fit line = -0.26 $\%^{-1}$.

V. Summary

- Test re-test repeatability was high. Inter-subject variability of high-luminance ppERG responses are comparable to conventional (ISCEV standard) pERG responses (CV = 18 and 11 for ppERG and pERG, respectively [Otto and Bach, 1997]).
- On average, the ppERG response component **N** decreased more rapidly (-1.0 μV RPS^{-1}) with reversal rate than N95 in conventional pERG (-0.3 μV RPS^{-1} for normal subjects from 2-7 RPS, reported by Berninger and Schuurmans [1995]).
- High frequency ppERG response components were relatively insensitive to reversal rate over the range investigated .
- The ppERG **P** and **N** components were slightly (not significantly) larger in the temporal field (nasal retina), which may reflect the known nasal-temporal asymmetry in ganglion cell density [Curcio and Allen, 1990].
- Cluster analysis of the small subject / patient population studied here suggests significantly higher sensitivity of ppERG responses to glaucomatous damage compared to conventional pERG.

Acknowledgments

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