

Pattern electroretinogram parameters across mechanistic subgroups of macular disease: an exploratory analysis

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Abstract

Purpose

To determine whether pattern electroretinogram (PERG) parameters differentiate mechanistic subgroups of macular disease.

Methods

Exploratory secondary analysis of the Pattern Electroretinogram dataset from the Institute of Applied Ophthalmobiology (PERG-IOBA). The macular disease records were assigned to mechanistic arms based on routine clinical diagnosis, including dilated fundoscopy and Optical coherence tomography, and to finer subgroups. Right-eye Positive wave at 50 milliseconds (P50) and Negative wave peaking at 95 milliseconds (N95) amplitudes, N95/P50 ratio, and P50 peak time were compared by Kruskal–Wallis and pairwise Mann–Whitney tests with Cliff's δ effect sizes, Benjamini–Hochberg corrected within each parameter. Six pre-specified comparisons were then examined.

Results

Of 63 macular-disease records, 57 cases carried an assignable mechanism: 38 were RPE/photoreceptor, 9 were choroidal, 8 were autoimmune, and 2 were ischemic. The omnibus test was null for all four parameters after correction (smallest adjusted $p = 0.113$). One pairwise contrast survived within its parameter: the N95/P50 ratio separated choroidal from autoimmune disease ($\delta = -0.78$, adjusted $p = 0.017$), but not under correction across all twelve contrasts. Stargardt disease did not differ from the pooled remainder (smallest adjusted $p = 0.699$).

Conclusions

Within these group sizes, PERG parameters did not differentiate mechanistic subgroups of macular disease. A revealed a higher N95/P50 ratio in autoimmune than in choroidal disease carries diagnostic potential but requires replication due to the number of records and the most permissive correction family.

Introduction

There is a rising interest in the pattern electroretinogram, which distinguishes macular from ganglion cell dysfunction by the relative behavior of its P50 and N95 components [1, 2]. While retinal function testing has been used to classify macular degeneration phenotypes [3], PERG abnormalities were described in inherited maculopathy [4]. At the same time, differentiating subgroups of maculopathy, which would bring clinical value for ophthalmologists, has not been found in the scientific literature.

As differences in the etiology of maculopathy affect structural and functional changes at the molecular level, it creates the possibility of detecting these alterations via PERG. That is why it became important for us to explore whether PERG can have a broader application and differentiate macular conditions by etiology.

The open-access PERG-IOBA dataset contains 63 macular-disease records acquired to ISCEV specification at a single institute [5, 6]. We used them to ask whether PERG parameters differentiate mechanistic subgroups, and to examine six comparisons of clinical interest. The analysis is exploratory and was powered by what the dataset contained rather than by design.

Methods

This is an exploratory cross-sectional secondary analysis of an open-access dataset, reported in accordance with STROBE [7]. The PERG-IOBA dataset comprises 336 records from 304 individuals evaluated at the Institute of Applied Ophthalmobiology, University of Valladolid, from 2003 to 2022 under approval 2021/47 of its research commission [5, 6]. Signals were recorded binocularly on a Vision Monitor MonPack 120 (Metrovision, Pérenchies, France) following ISCEV guidelines [1] and sampled at 1700 Hz over a 150 ms epoch.

P50 was measured as the maximum amplitude within a 35–65 ms window and N95 as the maximum negative deflection within a 75–130 ms window, each relative to the pre-stimulus baseline. This departs from the ISCEV convention of measuring P50 from the N35 trough and N95 from the P50 peak [1], because the dataset supplies averaged traces without marked component boundaries. Absolute amplitudes are therefore not interchangeable with conventionally measured values, but the same algorithm was applied to every record, so between-group comparisons are unaffected.

Records with a primary macular diagnosis were assigned to one of four mechanistic arms (RPE/photoreceptor, choroidal, autoimmune, ischemic) and, within the RPE/photoreceptor arm, to finer subgroups.

The macular disease records were assigned to mechanistic arms based on routine clinical diagnosis, including dilated funduscopy and Optical coherence tomography. Diagnoses were based on routine clinical assessment by ophthalmology specialists and clinicians at the Institute of Applied Ophthalmobiology (IOBA) at the University of Valladolid in Spain, between 2003 and 2022 [5]. The mapping was fixed before the outcome was examined and transferred to Online Resource 1 in the arms to be reconstructed from the public dataset. Arms with fewer than five records were reported descriptively and excluded from testing.

Right-eye parameters were compared across arms by Kruskal–Wallis test, with pairwise Mann–Whitney tests and Cliff's δ effect sizes with bootstrap confidence intervals. Benjamini–Hochberg correction was applied within each parameter across the three contrasts it contains. This is the most permissive, defensible family; correcting across all twelve pairwise contrasts instead raises the smallest adjusted

value from 0.017 to 0.066, and we report both. Intervals from a group smaller than ten were flagged as approximate, because the percentile bootstrap is anticonservative at those sizes; where an interval and a corrected p disagree, the corrected p governs. No a priori sample size calculation was possible. Analyses utilized Python 3.12 with pandas, NumPy, SciPy, and statsmodels. The analysis code is available from the corresponding author on reasonable request.

A large language model assisted with drafting the analysis code and manuscript text. All analytical decisions, verification, and final content are the authors' responsibility.

Results

Of 63 macular-disease records, an assignable cause was identified in 57 cases: 38 originated from the RPE/photoreceptors, 9 from the choroid, 8 from autoimmune conditions, and 2 from ischemia. The RPE/photoreceptor arm comprised Stargardt disease (23), other RPE/photoreceptor dystrophies (7), vitelliform spectrum (5), and pattern dystrophy (3). The two ischemic records, one acute macular neuroretinopathy and one paracentral acute middle maculopathy, are descriptive only. Distributions are given in Table 1 and Fig. 1.

The omnibus comparison across the three testable arms was null for all four parameters after correction (Table 2). The N95/P50 ratio gave the smallest unadjusted value, 0.028, which did not survive correction across the four-parameter family (adjusted $p = 0.113$).

Among the twelve pairwise contrasts, one survived correction: the N95/P50 ratio was higher in autoimmune than in choroidal disease ($\delta = -0.78$, unadjusted $p = 0.006$, adjusted $p = 0.017$), with medians of 2.01 and 1.37, respectively. The same parameter separated autoimmune from RPE/photoreceptor disease in the same direction but did not survive correction ($\delta = -0.43$, adjusted $p = 0.091$). No contrast on P50 amplitude, N95 amplitude, or P50 peak time survived; the smallest adjusted p across those nine comparisons was 0.368.

The six pre-specified comparisons are summarised in Table 3. Stargardt disease did not differ from the pooled remaining subgroups on any parameter, the smallest adjusted p being 0.699; at 23 versus 23 this was the best-balanced comparison available. Pattern dystrophy could not be tested at three records. In the vitelliform comparison, two bootstrap intervals excluded zero (P50 amplitude $\delta = +0.44$ and N95/P50 ratio $\delta = -0.53$), while neither test survived correction. With five records in the smaller group, these intervals are approximate and not positive findings.

The single surviving contrast required a Cliff's δ of 0.78, close to complete separation. Smaller effects were not resolvable at these group sizes.

Discussion

The revealed fact that PERG across mechanistic subgroups of macular disease was largely undifferentiating indicates that the small differences in action potential shifts go beyond the scope of detection with PERG. The omnibus test was null on every parameter after correction; the best-powered comparison available, Stargardt disease against the pooled remainder, was null; and eleven of the twelve pairwise contrasts did not survive correction.

The previously unreported elevation of the PERG N95/P50 ratio in autoimmune retinopathy to choroidal disease is consistent with the disease's pathophysiology. Presenting with photoreceptor dysfunction on electroretinography [8], it reduces P50 while leaving ganglion cell activity comparatively spared, thereby raising the ratio. It rests on 8 (autoimmune) and 9 (choroidal) records and survives within its parameter but not across all twelve contrasts. A large effect within groups of that size, surviving only the most permissive correction, is the configuration in which a spurious result is most likely. We report it as a hypothesis for replication, not a differentiating feature.

Because these are the comparisons most likely to be attempted on a small clinical series and abandoned when null, the bounded negatives reported here are the more durable contribution.

Limitations bound the interpretation. The subgroups are small by construction, and several comparisons involve three to nine records. At the same time, it is more beneficial in clinical practice to compare diagnoses with similar presentations that are hard to differentiate. This is why we chose to study these specific groups to help clinicians distinguish between them.

In addition, the assignment is based on clinical diagnoses recorded during routine care, without genetic confirmation, and phenotypic overlap among some of the disorders is substantial, as variants in a single gene can produce pattern, vitelliform, and choroidal dystrophies in different individuals [9, 10]. Ocular dominance, which affects P50 amplitude [11], was not recorded, and only right eyes were analysed. At the same time, right-eye dominance prevails in most humans, and changes in dominance are possible [12]. These facts diminish this limitation.

The dataset is public [6], and the arms defined here are reproducible from it; therefore, non-genetically confirmed subgroups are compared. Despite limitations, the correlation revealed by PERG between two maculopathy subgroups suggests the potential for wider clinical application of PERG, especially with the further development of PERG in the future.

Declarations

Competing interests

The authors declare that they have no competing interests.

Ethics approval

This is a secondary analysis of a publicly available, fully de-identified dataset and involved no new contact with participants. The original data collection was approved by the research commission of the Institute of Applied Ophthalmobiology, University of Valladolid (approval 2021/47), and adhered to the tenets of the Declaration of Helsinki. No further approval was required.

Consent to participate

Participants in the original data collection were informed at the time of testing that their data might be used for research.

Consent to publish

Not applicable. The dataset is fully de-identified.

Data availability

The data are publicly available from PhysioNet as the PERG-IOBA dataset, version 1.0.0, at <https://doi.org/10.13026/d24m-w054> [6], under the Open Data Commons Attribution License v1.0, which requires attribution. The dataset is described in its accompanying data descriptor [5], and the PhysioNet platform citation is given at reference [13]. The analysis code is not deposited in a public repository; it can be shared by the corresponding author upon reasonable request.

Related work

Two companion analyses of this dataset, addressing the N95/P50 ratio across diagnostic categories and the relationship between P50 amplitude and visual acuity, are reported separately. All three share a cohort and a recording protocol but address different questions; none duplicates the results of the other.

Author contributions

Conceptualization: Farida Mehrhoff; Methodology: Farzad Haji Boloori; Formal analysis and investigation: Farzad Haji Boloori; Writing – original draft preparation: Farzad Haji Boloori; Writing – review and editing: Farzad Haji Boloori, Bailey Nelson, Farida Mehrhoff; Supervision: Bailey Nelson, Farida Mehrhoff. All authors read and approved the final manuscript.

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Figures

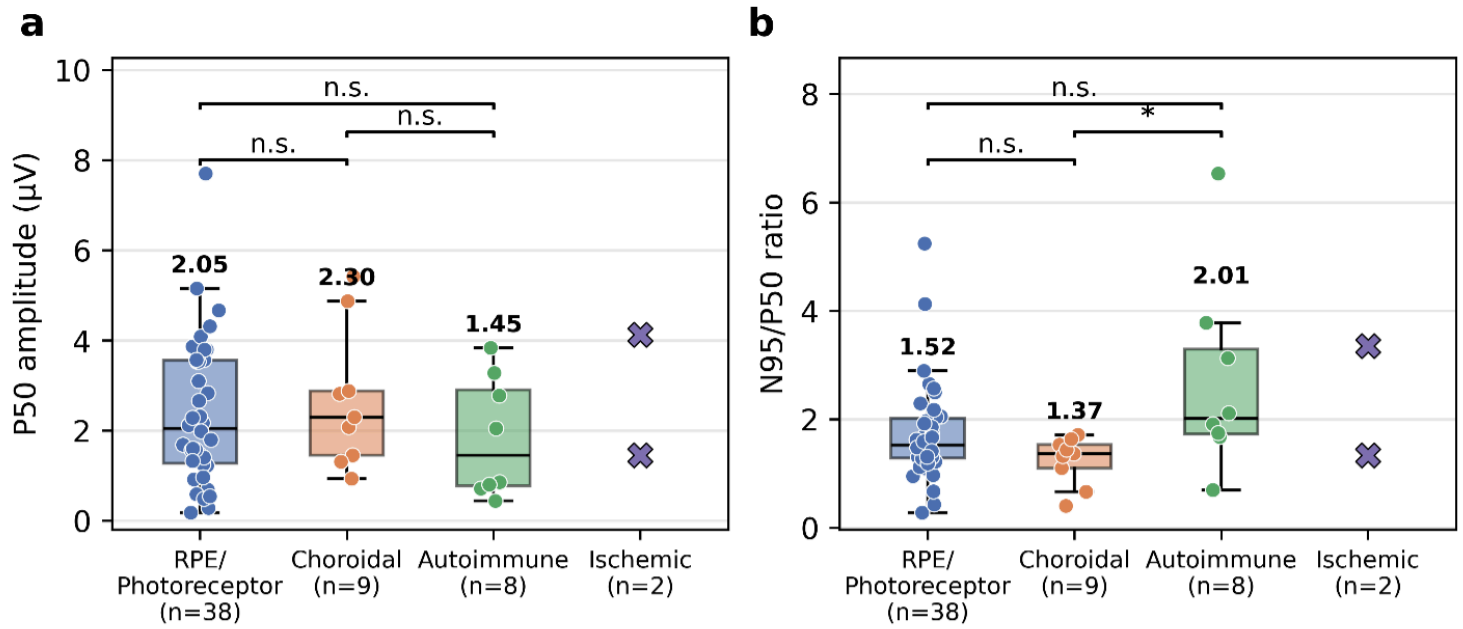


Figure 1

PERG parameters across mechanistic arms of macular disease. **a** P50 amplitude. **b** N95/P50 ratio. Boxes show the interquartile range, the horizontal line the median, and dots individual records; the bold number above each box is the group median. Ischemic cases are shown as individual markers and were excluded from testing. Brackets give the Benjamini–Hochberg adjusted Mann–Whitney p-value within each parameter, where a single asterisk denotes $p < 0.05$ and n.s. denotes not significant