

Update on the Pattern Electroretinogram in Glaucoma

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Abstract

Purpose. To review the efficacy of the pattern electroretinogram (PERG) in early diagnosis of glaucoma.

Methods. Stimulation parameters of check size and temporal frequency are considered. Analyses of various peaks (P50, N95, the N95/P50) and Fourier steady-state are considered. The relation to visual field defects is explored.

Results. The PERG is markedly altered in glaucoma. It shows amplitude reductions in (still) normal areas of the visual field. Optical imaging on the retina needs to be optimal. Higher temporal frequency (>10 reversals/s) improves the sensitivity to detect glaucoma compared to transient stimulation. The ratio between the amplitudes to 0.8° checks and to 16° checks, “PERG ratio”, exploits a check-size specific reduction in early glaucoma and reduces variability. Longitudinal studies suggest that the PERG can indicate incipient glaucoma damage before evidence from the visual field.

Conclusions. The PERG is a demanding electrophysiological technique that can serve as a sensitive biomarker for retinal ganglion cell function. With appropriate paradigms, PERG assists in identifying those patients with elevated IOP in whom glaucoma damage is incipient before visual field changes occur.

Key words

glaucoma; diagnosis; electrophysiology; pattern electroretinogram; PERG

Course of glaucoma and the importance of early detection

Glaucoma starts when communication between the ganglion cell axons and the ganglion cell body is compromised, either mechanically or due to vascular impairment, near the optic disc. Ultimately the ganglion cells atrophy, be it through necrosis or apoptosis, while bipolar cells and the photoreceptors remain nearly normal. Until a decade ago glaucoma was almost synonymous with raised interocular pressure (IOP), then importance of IOP became de-emphasized to the

degree that it was no longer mentioned in glaucoma definitions (see¹ for a review). More recently, the tables were turned again due to the completion of a number of longitudinal multi-center studies, namely the Early Manifest Glaucoma Trial² and the Ocular Hypertension Treatment Study³. Briefly, these studies suggest that (1) the progression of glaucoma is indeed slowed down by reducing IOP (rule of thumb: 1 mmHg reduction reduced risk of damage progression by 10%) and (2) the conversion from ocular hypertension (OHT) to manifest glaucoma is reduced by reducing IOP.

Even while elevated IOP thus is a major risk factor for developing glaucoma, only about 1% of patients with an IOP of 25 mmHg actually do develop manifest glaucoma each year. Prospective studies have reported incidences ranging from 0.4% to 17.4%⁴⁻⁹. This wide range is largely due to differing study populations with different risk factors or degrees of pressure elevation. Since a sizeable proportion of the ganglion cells, i.e., 25-30%, is already lost when visual field losses are apparent^{10,11}, the aim of early detection is to identify those patients with elevated IOP who have early stage glaucoma damage before visual field changes occur. Thus therapy can be applied before irreversible retinal damage and visual field loss has occurred, while sparing patients who have “just” an elevated IOP. Early detection could well profit from electrophysiological techniques as demonstrated in the present review.

Magnocellular vs parvocellular pathways – not of major relevance in glaucoma

Research on early diagnosis has been dominated for more than a decade by the “magnocellular paradigm”, starting with Quigley’s observation¹²: “in early glaucoma ... [there is] preferential damage to large nerve fibers”. Previous sub-divisions of the visual pathway had been based on psychophysical intricacies¹³, but Quigley’s observation came at a time when division of the visual system into (at least) two major sub-systems was rekindled^{14,15}. The two major sub-systems that Quigley et al. considered for the selectivity of early glaucoma damage were the magnocellular stream, with large axons, making it the candidate for Quigley’s observation, and the parvocellular stream, which was presumed to be relatively spared. This clear-cut hypothesis had two major consequences: Firstly, it spurred basic scientists to challenge this simple view, to find exceptions, and to test the limits of its applicability. Secondly, it led some applied researchers to oversimplified¹⁶ stimulus paradigms aiming at a selective stimulation of the magnocellular

system. For more than a decade, research on early diagnosis of glaucoma was dominated by this “magnocellular damage paradigm”. While it inspired interesting methodological developments, many researchers now feel that magnocellular damage in early glaucoma is only marginally greater – if at all – than parvocellular damage¹⁷. Recent work is unequivocal on this: Crawford, comparing psychophysical findings, reported no evidence for specific magnocellular damage¹⁸, and Yücel, using an experimental glaucoma model, found both magno and parvo loss in the lateral geniculate nucleus, if anything there was more parvo loss^{19,20}. Finally, the well-known early blue deficits in glaucoma²¹ cannot readily be conciled with a magnocellular mechanism. In summary, the hypothesis of “preferential magnocellular damage in early glaucoma” is not a valid guideline. As a consequence, specifically targeting the magnocellular system in glaucoma research is not topical any more. Efforts of electrophysiological investigations may therefore concentrate on other issues, such as the isolation of retinal ganglion cell activity and the reduction of signal variability.

Targeting retinal ganglion cell function with visual electrophysiology

Visual electrophysiology commands a broad arsenal and nearly each of its methods has been applied to glaucoma (for an authoritative recent review see ²²). For each of the various processing stages that a visual input passes through, there is an investigative technique to assess functional integrity. The targets of electrophysiological investigation of glaucoma are threefold, namely: (1) early diagnosis, (2) monitoring the course of the disease, and (3) furthering our understanding of the pathophysiological mechanisms. When we consider the pathophysiology of glaucoma, it is not surprising that many of the techniques used in visual electrophysiology have had little success. Stages prior to the ganglion cells are comparatively unaffected especially at the onset of glaucoma. The pattern electroretinogram (PERG) reflects ganglion cell activity itself and is therefore a direct and promising approach to assist early detection of glaucoma. While this method is the topic of the present review, we wish to indicate that other electrophysiological approaches to investigate glaucoma have also attracted attention: (1) The Photopic Negative Response (PhNR)^{23,24}, a novel promising retinal signal, is under testing in various laboratories to determine its value in early glaucoma detection. (2) The S-cone VEPs²⁵ appear to reflect psychophysical findings which demonstrated that the S-cone (koniocellular²⁶) pathway appears to be affected by glaucoma before standard subjective perimetry is affected²⁷. A delay of these VEP

responses may precede morphologically evident glaucomatous damage by two years²⁸. The S-cone ERG also shows alteration in glaucoma²⁹. (3) Multifocal pattern-reversal VEPs prove to be useful for the objective assessment of visual field loss caused by advanced glaucoma^{30, 31}. Some potential for early detection of glaucoma has been attributed to this technique³², but recently a similar diagnostic performance of mfVEP and standard automated perimetry was reported³³. (4) Experience with the conventional VEP suggests that it might not be of major relevance for the early detection of glaucoma as conventional pattern-reversal VEPs are less affected by glaucoma than PERGs (e.g., ³⁴). This can be understood on the grounds that VEPs do not tap the primary locus of glaucoma-caused damage, but reflect the activity of later stages in the visual processing chain which are subject to gain control – possibly masking early changes – between retinal ganglion cell activity and cortical response³⁵⁻³⁷.

PERG basics

The pattern ERG (PERG) is a direct indicator of ganglion cell function³⁸ (for a detailed review see³⁹) and thus a promising candidate to indicate early glaucoma damage. The methodology is only briefly covered here, more detail can be found in the ISCEV PERG standard⁴⁰. As stimulus a checkerboard pattern is used, which reverses its local luminance while keeping average luminance constant. Thus, the ERG signals cancel out and non-linearities remain that have been shown to originate mainly in the ganglion cells⁴¹⁻⁴⁵. Retinal potentials are detected with a corneal electrode. Various types of electrodes may be used, such as gold foil^{46, 47}, DTL⁴⁶ or HK-Loop⁴⁸. In contrast to recording the ERG, is very important that the electrode does not degrade the optical image on the retina, as reduced retinal contrast leads to a marked reduction of the PERG⁴⁹⁻⁵¹. With an appropriate technique, a high stability and reproducibility can be obtained (we found the inter-session coefficient of variation is approximately 10%⁵²).

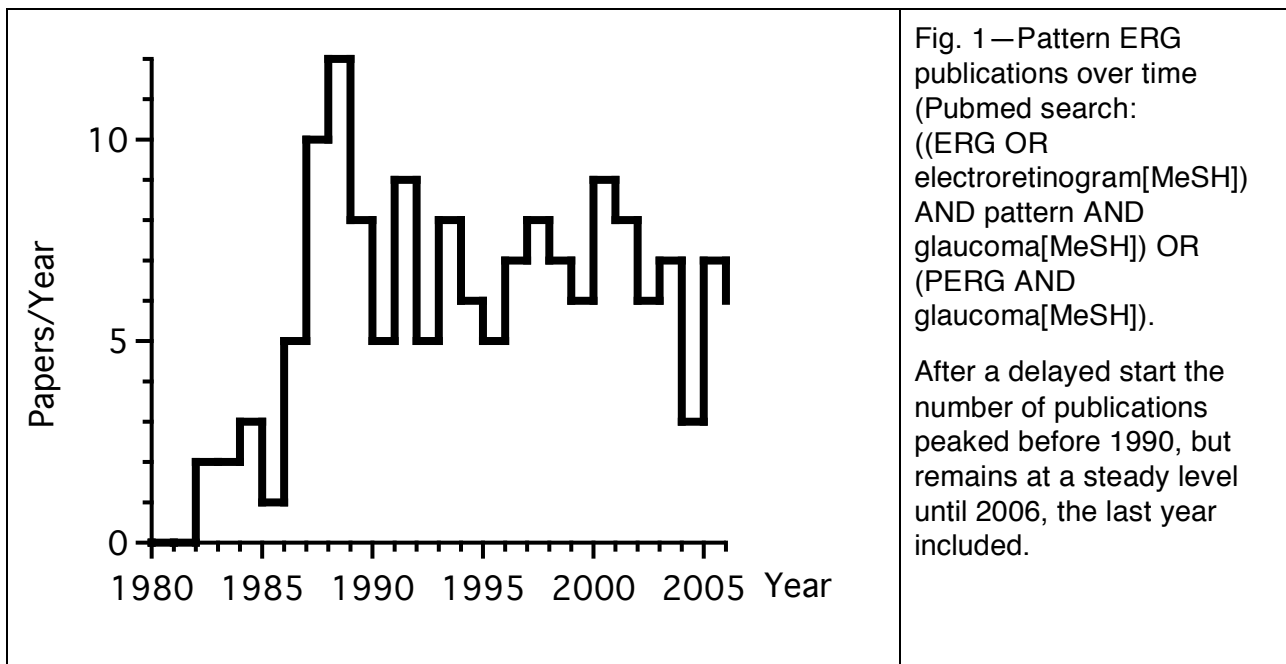
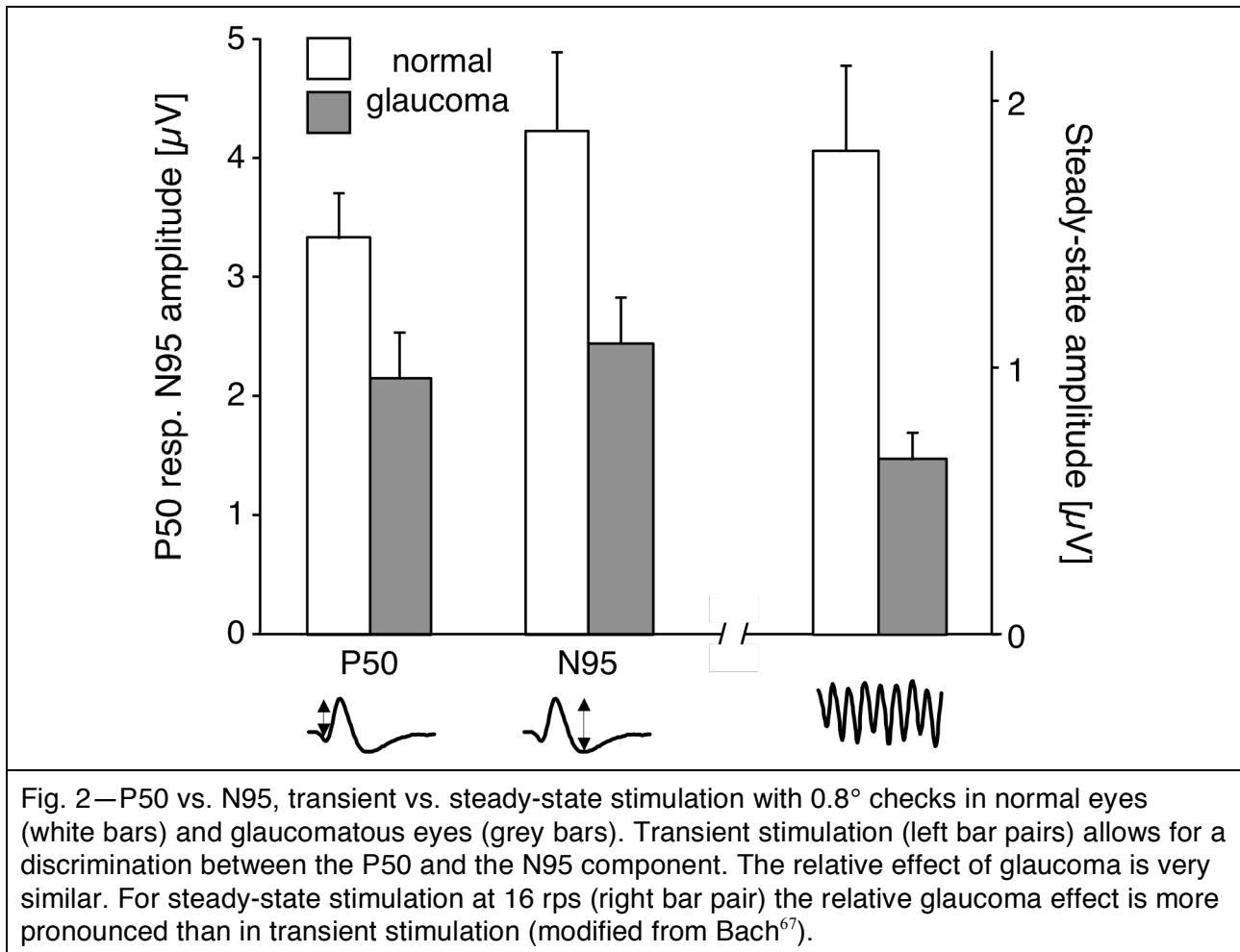


Fig. 1 — Pattern ERG publications over time (Pubmed search: ((ERG OR electroretinogram[MeSH]) AND pattern AND glaucoma[MeSH]) OR (PERG AND glaucoma[MeSH]).

After a delayed start the number of publications peaked before 1990, but remains at a steady level until 2006, the last year included.

History of PERG in glaucoma

The first paper reporting PERG recordings in a glaucoma patient was by May et al. in 1982⁵³. In 1983, two papers appeared, namely by Bobak et al.⁵⁴ and the first of Wanger and Persson's seminal work with 11 patients⁵⁵. This initiated a steady stream of reports (Fig. 1) that is still going strong (e.g.,^{56,57-73}). All but one of these papers reported PERG amplitude reduction in glaucoma without sizable effects on latency. The one exception is a study by van den Berg et al.⁷⁴, who did not find a correlation between visual field loss and PERG amplitude, which can in hindsight be understood as a consequence of the experimental design applied: In order to reduce interindividual variability, the authors used the fellow eyes as reference. However, the incidence of glaucoma in the fellow eye is very high and PERG reduction seems to precede obvious visual field loss (see below). It is likely, therefore, that in van den Berg's study the PERG amplitudes were also reduced in the reference eye, thus the effect of glaucoma did not show up in the interocular difference.



P50 vs. N95, Steady-state vs. transient responses

The frequency of the checkerboard reversal determines whether the transient response (< 4 rev/s) or the steady-state response (≥ 8 rev/s) is evoked (see the ISCEV PERG standard⁷⁵). When the transient PERG is recorded, a positive (P50) and a negative (N95) component can be discerned. These can be affected differently in retinal and optic nerve diseases³⁸. When reducing the spiking activity of ganglion cells by application of Tetrodotoxin in macaque monkeys, Viswanathan et al. found a reduction of the P50 down to 60%, of the N95 down to 23%²³. Hood et al.⁷⁶ reported an overlap of controls and patients for both the N95/P50-ratio and the N95 raw amplitude, which was more pronounced for the ratio [a ratio of ~ 1.5 (range 1.2–1.9) for normal controls and a ratio of ~ 1.3 (range 1.1–2.1) for glaucoma patients]. Our own data indicate that the P50 and N95 are rather similarly reduced: In a group of eight normal control eyes and 23 eyes of 12 glaucoma patients, the PERGs to transient stimulation and to steady-state stimulation were compared. Fig. 2 shows that in the transient response, the P50 and the N95 component were affected rather

similarly by glaucoma. In contrast, the steady-state response is relatively much more affected by glaucoma, rapid stimulation at 16 rev/s showed a much more pronounced amplitude reduction than did transient stimulation, when compared in the same glaucoma patients (right of Fig. 2⁶³). When reversal rates become higher than 18 rev/s, the PERG becomes less effective for discrimination between normal and glaucoma, probably because, probably because of decreasing signal/noise ratio⁷⁷. These frequency-dependent effects have also been shown by Trick⁷⁸ and correspond well with psychophysical work that showed more glaucomatous effects at higher temporal frequencies^{25, 79, 80}.

Altogether, the evidence of three studies suggests that steady-state PERG recording at temporal frequencies between 10 and 20 rps is most efficacious for detecting incipient glaucoma damage^{63, 77, 78}. The higher sensitivity of the PERG to early glaucoma using high temporal frequencies seems important for any clinical study design and deserves a more thorough investigation. Stimulation frequencies in the steady-state region (above ≈ 6 rev/s) have additional technical advantages: (1) they lend themselves to automatic analysis once the intricacies of Fourier analysis are mastered, and (2) there is less degradation by eye movements or blinks; to record a reliable transient N95 one must employ demanding procedures⁸¹.

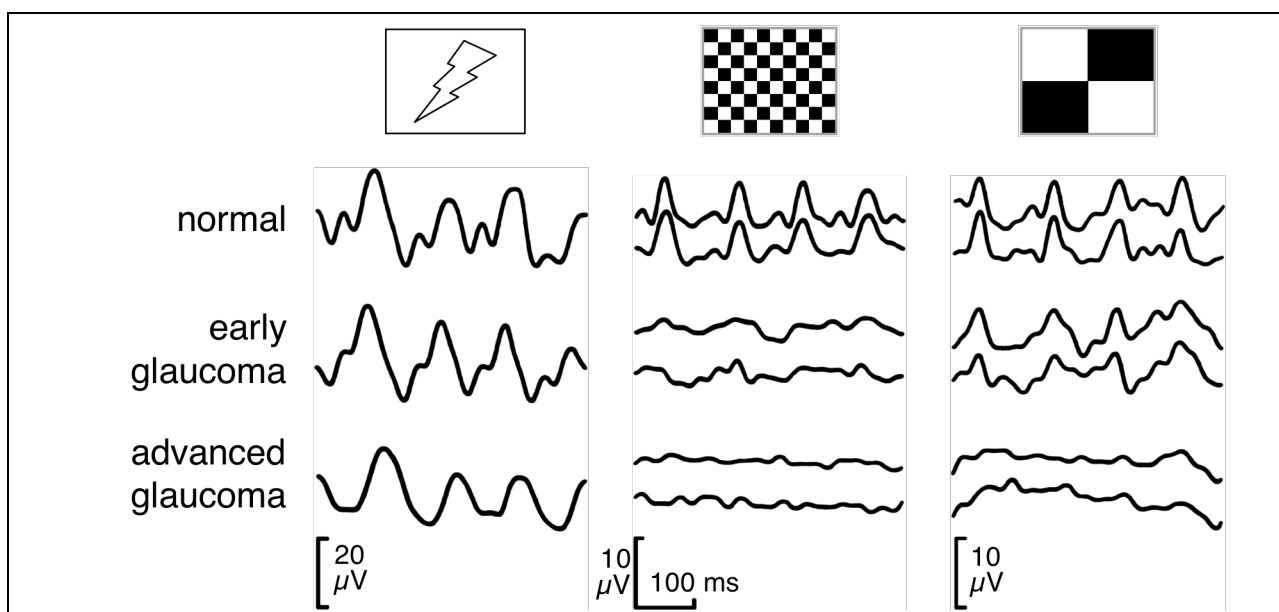
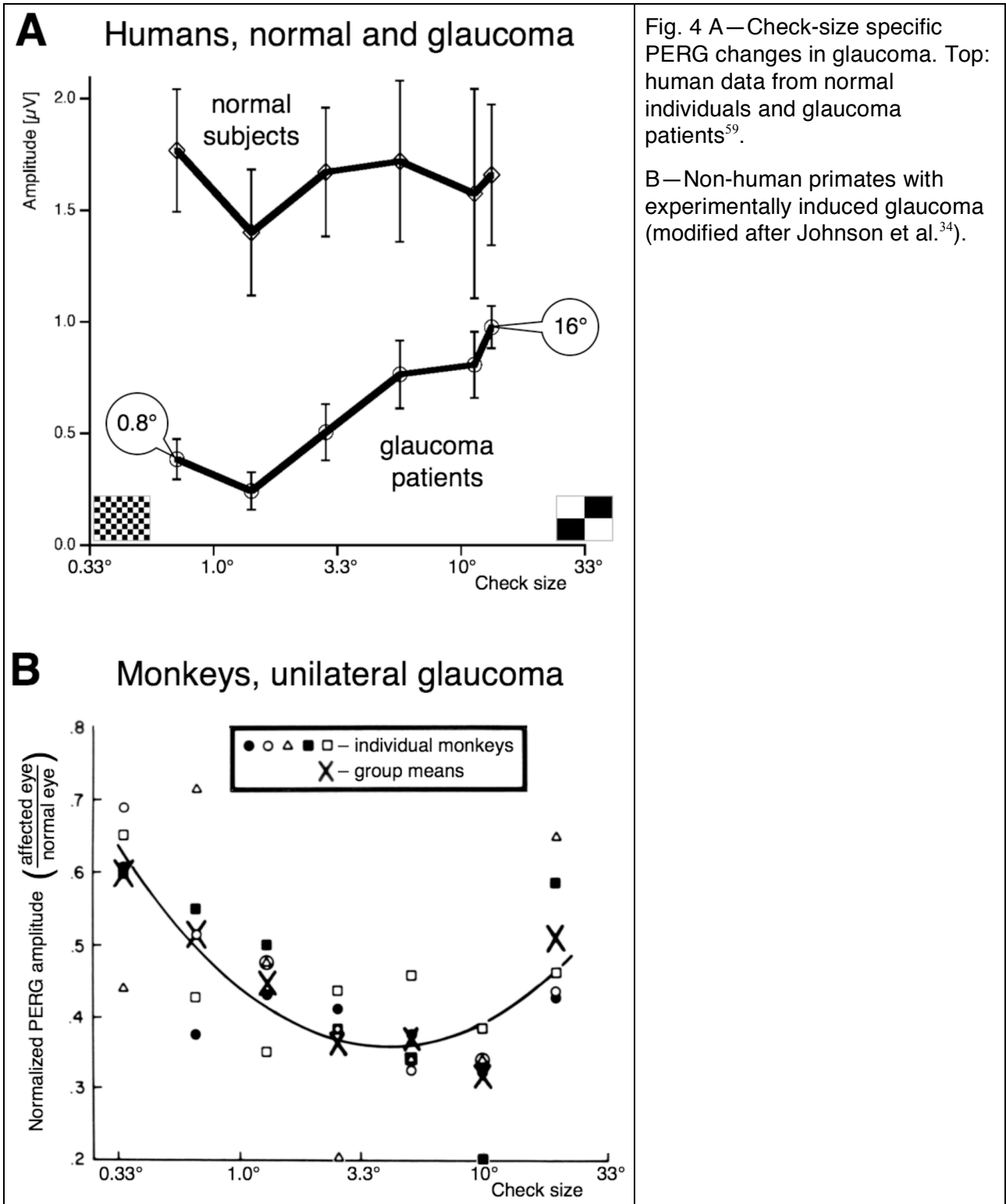


Fig. 3—ERG & PERG in glaucoma. The flash ERG (left column) is relatively little affected, even in advanced glaucoma. In early glaucoma (center row), there is a sizable reduction of the PERG to 0.8° checks and little reduction for 16° checks. In advanced glaucoma (bottom row), the PERG to any check size is reduced (modified after Bach et al.⁵⁹).



Checksize-specific PERG reduction in early Glaucoma

The PERG to large stimulus checks is relatively spared in early glaucoma. This is illustrated in Fig. 3, where recordings from a normal individual, a patient with early glaucoma, and a patient

with advanced glaucoma are depicted⁵⁹. In the left column, ERG responses to a flash stimulus show little change in glaucoma (they do, however, show a shape difference which may be related to a reduced PhNR as discussed in “Targeting retinal ganglion cell function” above). In contrast, the PERG to small check sizes (0.8°, center column) is affected in early and late glaucoma, whereas the PERG to large stimulus checks (16°, right column) is relatively normal in early glaucoma, but markedly reduced in the advanced stage of the condition.

The check size specific effect is shown in Fig. 4 in further detail. At the top, there are findings from 15 glaucoma eyes, while results from experiments with experimentally induced glaucoma in monkeys are depicted at the bottom³⁴. Both experiments show that the PERG to large checks is relatively little affected in early glaucoma, with increasing effect with decreasing check size. Similar examples are found in Zrenner et al.⁸². There is also an indication that with very small checks (< 0.5°) the glaucoma effects become smaller again as also reported by Trick⁷⁸. These differential effects of check size have useful implications when using the PERG in early diagnosis of glaucoma as will be detailed in the following section.

“PERG ratio” paradigm for glaucoma

Highly significant group differences in the PERG amplitude between normal controls and glaucoma patients do not necessarily imply that a useful risk assessment can be performed on an individual basis. In group comparisons, the high inter-individual variability can be counteracted by high case numbers. For individuals, the results need to be compared to the population distribution, where an octave up or down comprises the 95% confidence interval⁸³. To tackle this problem, the Freiburg group arrived at the following paradigm. Firstly, steady-state stimulation of 16 rev/s is employed. This frequency is believed to be in the optimum range as described in a preceding section. The exact reversal rate also depends on the equipment, as aliasing by the frame rate of the stimulus monitor must be avoided⁸⁴. Secondly, we combine two check sizes, 0.8° and 16°. Recalling Fig. 3, we note that the PERGs to 0.8° checks are strongly affected by glaucoma, whereas the PERGs to 16° checks are less affected. The interindividual variability is multiplicative⁵², such that an individual with a large 0.8°-PERG will also have a large 16°-PERG. Thus it makes sense to compute the ratio:

$$PERG\ ratio = \frac{PERG\ amplitude\ to\ 0.8^\circ\ checks}{PERG\ amplitude\ to\ 16^\circ\ checks}$$

In Fig. 5, the scatter of a normal control population is seen (data extended from ⁸⁵). There is a high correlation between the amplitudes to 0.8° and 16° check size in normals. In glaucoma, this correlation is decoupled as described in the previous section: initially the 0.8°-response is reduced, then later the 16°-response. Consequently, an untreated or treatment-resistant glaucoma eye will likely follow the hypothetical curve indicated by the curved dashed arrow in Fig. 5. A constant PERG ratio of 1.0 corresponds to the 45°-line in this figure (the slight difference in amplitude between the two check sizes is factored out here by age normalization). For individual diagnosis, the lower and upper lines indicate the 5% and 95% confidence interval for the PERG ratio, respectively. PERGs from individual eyes that fall below the lower confidence line may be at risk of developing glaucoma (more on this in the section on longitudinal studies below).

As attractive as the ratio approach may seem, there are two caveats to be kept in mind: First, As with any ratio approach (as used, for instance, in the EOG Arden ratio, or the b/a-wave ratio in the ERG), a ratio becomes unreliable when the denominator becomes too small. Thus, for advanced stages of glaucoma, the PERG ratio will lose value as a surrogate marker. Second, the PERG ratio can be visualized as a projection of all data points on a line orthogonal to the 45° line in Fig. 5. Along this line some interindividual variability remains. As the time course of the disease starts vertically down, part of the variability is projected onto the disease course, and the PERG ratio loses some of its advantage – though it still improves on evaluating the 0.8° amplitude alone (see section on longitudinal studies below).

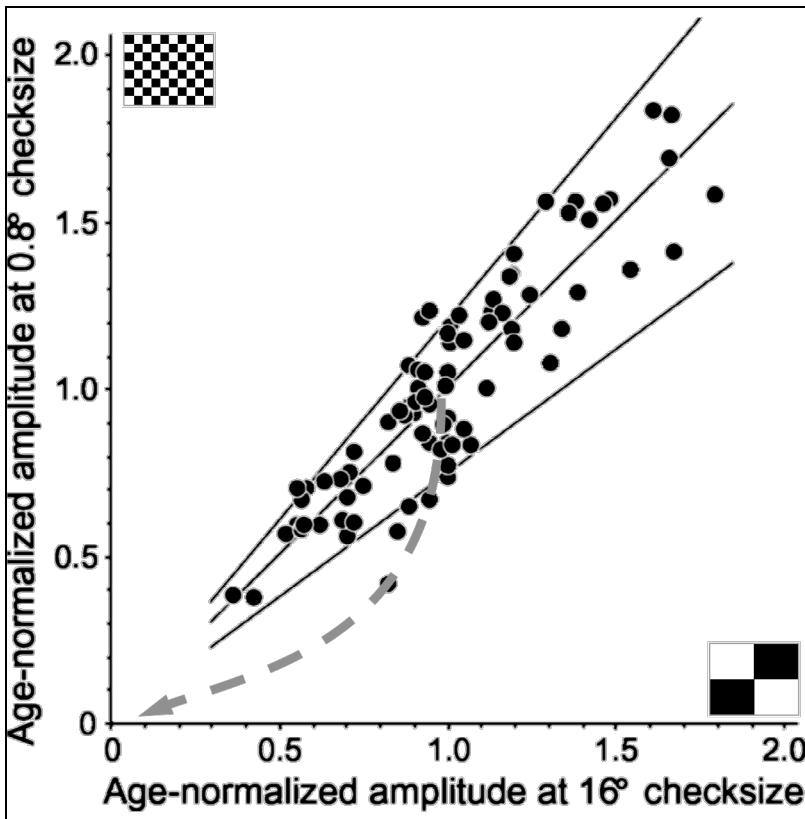


Fig. 5—PERG amplitudes to two check sizes ($0.8^\circ / 16^\circ$) in 85 normal eyes. A wide scatter of amplitude between individuals is seen.

The mean course of disease is likely to follow the grey dashed arrow.

The “PERGLA” paradigm

Another well-standardized paradigm to employ the PERG in glaucoma is the one called “PERGLA” by the authors, Porciatti and Ventura⁸⁶, for a review see⁸⁷, a commercial system is available. A main feature of their approach is the use of skin electrodes, which avoid the contact to the cornea. The use of a grating rather than a checkerboard is a minor difference, the dominant spatial frequency is very similar to a 0.8° -checkerboard. The value of this approach has been demonstrated in glaucoma⁷³, also from an independent laboratory⁸⁸, and was found to be sensitive in detecting pressure-related changes⁸⁹. Using a skin electrode certainly feels less invasive to the patient. The amplitude is lower (about a factor of 3, widely differing between subjects), but that is of no matter, as intrusions from eye movements are also lower. We found the signal-to-noise ratio of skin electrodes only marginally below the one obtained by DTL electrodes (unpublished observation). The PERGLA paradigm and the PERG Ratio described above do not really differ in their essence and could be easily combined. In table 1 some details can be compared. Clearly an investigation comparing the PERGLA approach to others is warranted.

Table 1. Comparison of two standardized PERG-glaucoma paradigms		
	PERGLA	PERG Ratio
Type of stimulus	Grating	Checkerboard
Temporal frequency: Steady-state	√	√
Fine stimulus (checkerboard 0.8° or grating 2 cpd)	√	√
Coarse stimulus	—	√
Electrode type	Skin	Cornea (DTL)
Fourier analysis employed	√	√
Check-size specificity employed	—	√
Normal data available	√	(√)
Independent confirmation	√	—
Longitudinal value demonstrated	—	√

A caveat – effect of retinal image quality on PERG

Any degradation of retinal imaging (e.g. by cataract or defocus) leads to PERG amplitude reduction⁹⁰⁻⁹³. Dioptric defocus is the more problematic case here, since it affects the PERG evoked by 0.8° checks and not the PERG evoked by 16° checks⁵⁹, thus changing the PERG ratio in the same manner as glaucoma would. This is illustrated in Fig. 6, where visual acuity was reduced by dioptrical defocus, covering a decimal acuity range from 0.1 to 1.6. Increasing defocus markedly reduces PERG amplitude when 0.2° and 0.8° checks are employed, but has no significant effect with a 16° check size. Wide-angle scattering, as occurs with cataracts, also affects the 16°-response, leading to less marked effects on the PERG ratio. The effects are readily understood when the low-pass nature of defocus⁹³⁻⁹⁵ and the PERG's linear contrast-amplitude characteristic are taken into account^{49,51}. To avoid false positive results, we perform PERG-glaucoma testing only on eyes with a visual acuity ≥ 0.8 , tested at the PERG-stimulus distance of 57 cm with a semi-automatic procedure⁹⁶. While optimal optical correction is just a matter of diligence, unfortunately a number of glaucoma patients have beginning media opacities, thus precluding reliable interpretation of PERG findings in such cases.

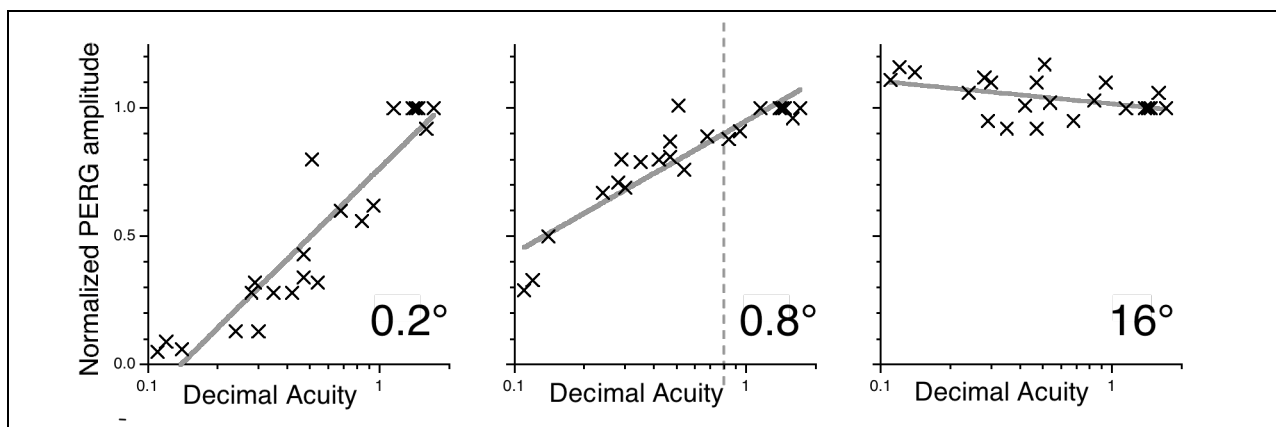


Fig. 6—Effects of dioptric defocus on the PERG amplitude in 10 eyes of visually normal subjects either at best correction or with various values of defocus. Check size increases from left to right. Check size of 0.8° (center column) is relevant for PERG in glaucoma. Based on these findings, we only view PERG results in glaucoma as valid when the visual acuity is ≥ 0.8 (arrow; modified after Bach et al.⁹³).

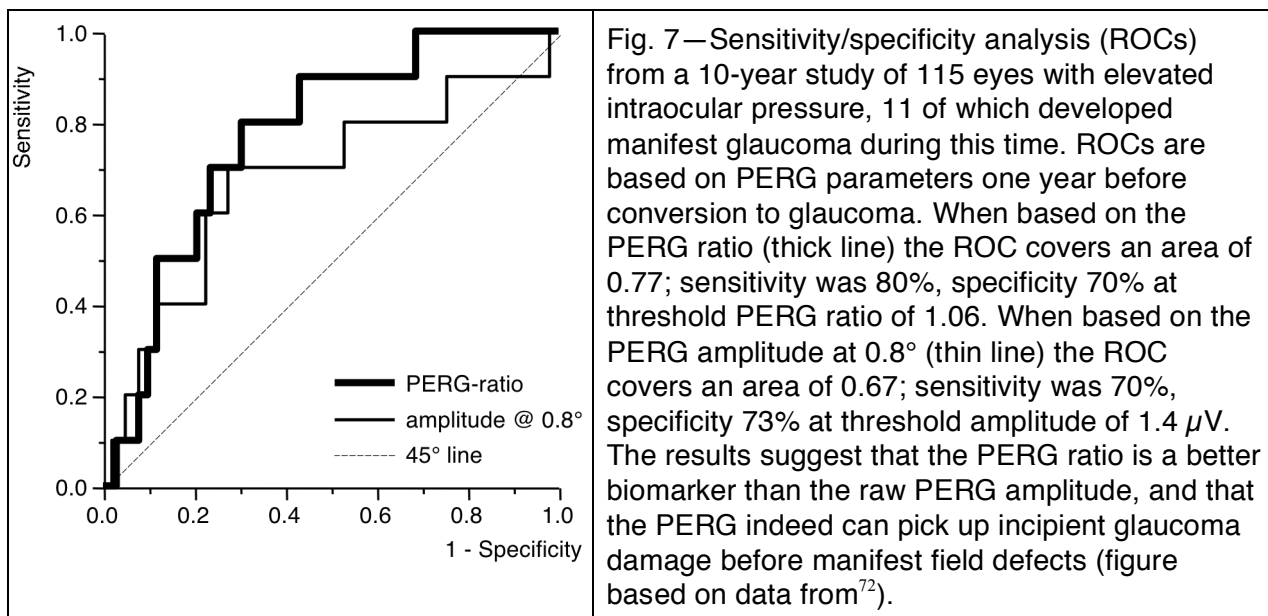
Predictive value of PERG in OHT – Longitudinal studies

In order to test the utility of the PERG as a biomarker for early glaucoma, longitudinal studies have been performed to test whether the PERG identifies eyes with elevated IOP that later develop manifest glaucoma. There is a relative scarcity of such studies, largely due to the need of long-term investment of sizeable resources in a time-varying clinical environment and the loss of patients to follow-up. In an early study, we addressed the problem by selecting high-risk eyes (e.g. glaucoma in the patient's other eye, family history) and recorded the history of 29 eyes in 18 individuals for 1 to 3 years⁶⁸. Initially, in 12 of these eyes the PERG was abnormal, and five of these eyes did develop glaucomatous field defects. In contrast, none of the eyes with initially normal PERG developed glaucomatous field defects.

In a more recent prospective study⁹⁷, we recorded the history of 95 eyes of 54 patients with initial IOP > 25 mmHg and no apparent visual field damage for up to 10 years (mean follow-up time 8.2 years). Over this time, 8 eyes of 5 patients developed manifest glaucoma. By varying the pathology-threshold of the PERG ratio (defined above), we compared the sensitivity and specificity of the technique. Based on the PERG ratio we found a ROC area of 0.78; sensitivity was 80% and specificity 71% at a threshold PERG ratio of 1.06. Based on the PERG amplitude at 0.8° (Fig. 7, thin line) we found a ROC area of 0.68. This sensitivity/specificity analysis (receiver operating characteristic, or “ROC”-analysis) one year before manifest glaucoma is depicted in Fig. 7 (data from an intermediate analysis⁷²). The results suggest that the PERG ratio is a slightly

better biomarker than the raw PERG amplitude, and that the PERG indeed can pick up incipient glaucoma damage before manifest field defects.

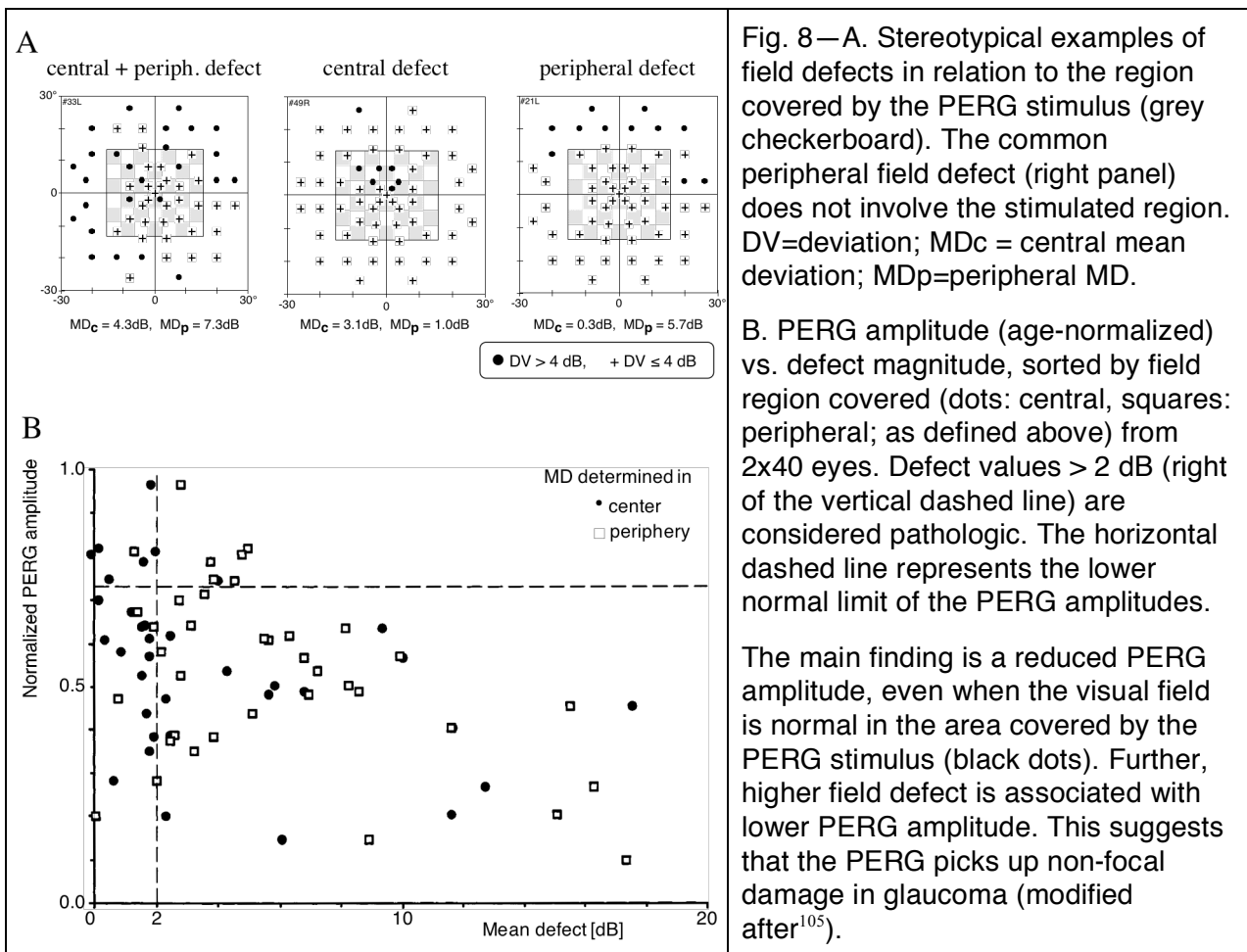
The matter clearly deserves more research, but the present data suggest that the PERG is of value in defining eyes that are at higher risk of developing manifest glaucoma.



PERG and “panretinal ganglion cell damage” in glaucoma

In hindsight it is unexpected for the PERG to detect glaucoma changes so effectively, considering that the stimulus covers only the central 15°, while early field defects arise typically in the more peripheral Bjerrum area. There was already indirect evidence that the PERG reflects diffuse, non-focal, damage to the ganglion cells⁸⁵, but to test this more directly we looked at the PERG in eyes that had no field damage within the retinal area covered by the PERG stimulus. An example of such a field is seen in Fig. 8A right. Fig. 8B shows PERG amplitude vs. field defect for the two field areas. When we restrict analysis to those patients where the center was normal but the mean peripheral defect was > 2 dB (right of the vertical dashed line), we find that most have pathological PERG amplitudes (below the horizontal dashed line), and some are normal. Evidently, and as recently confirmed⁷⁶, visual field loss and early ganglion cell damage are not congruent. This suggests that the PERG picks up a “panretinal” damage mechanism, which affects the ganglion cells before reliable field damage is observed. It is intriguing to investigate the spatial extent of the glaucoma-induced PERG-reduction with multifocal techniques, which allow one to record independent responses from a large number of visual field locations

simultaneously. In general, this is an ambitious approach, as PERG amplitudes from a 15° by 15° patch are already small, and will be reduced even further, if smaller patches are used for multifocal stimulation. As a consequence, multifocal PERG (mfPERG) studies are hampered by small signal-to-noise-ratios and ways to enhance the signal-to-noise-ratio of the mfPERG must be found to increase its value for the spatially resolved assessment of retinal ganglion cell function⁹⁸. To date, only few studies exist on the mfPERG in glaucoma⁹⁹⁻¹⁰². In these studies reduced mfPERG amplitudes are reported in glaucoma patients. Furthermore, they confirm that the amplitude reduction does not appear to be in a close topographical relationship to the visual field loss observed in these patients and thus support the above interpretation that the PERG is affected “panretinally” in glaucoma. Possibly, this panretinal mechanism mirrors the toxic effects of activated glia in the optic nerve head^{103, 104}. Currently, the value of the mfPERG would rather lie in advancing our understanding of the underlying pathophysiology than in early detection of glaucoma.



Conclusion

The PERG has shown to be of use in early diagnosis of glaucoma: With appropriate recording techniques and paradigms, it can identify eyes at risk one year before manifest field damage with a sensitivity and specificity of $>70\%$. It should be recognized that PERG recording is one of the more demanding electrophysiological techniques, and that experience and care is required to achieve reliable and reproducible results. Nevertheless, at the present state of knowledge the PERG is a promising electrophysiological technique for detecting early glaucoma damage. It is expected to assist the identification of those patients with elevated IOP in whom glaucoma damage is incipient before visual field changes occur.

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