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Michael Bach

Universitäts-Augenklinik, Freiburg, Germany

Address for correspondence:

Michael Bach

Elektrophysiology Lab

Universitäts-Augenklinik

Freiburg, Germany

Tel: ++49 (761) 270-4060 / 4061

Fax: ++49 (761) 270-4052 / 4063

Email: bach@uni-freiburg.de

www.ukl.uni-freiburg.de/aug/bach/

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ABSTRACT: While elevated intraocular pressure (IOP) is a major risk factor for glaucoma, only about 1% of patients with 25 mmHg develop the condition each year. Since a sizeable proportion of the ganglion cells is already lost when the visual field losses are apparent, the aim is to identify patients with elevated IOP in whom glaucoma damage is incipient before visual field changes occur. This report concerns early diagnosis of glaucoma with electrophysiological techniques, rather than with monitoring the disease using various available psychophysical and morphological methods. Visual electrophysiology offers a wide range of tools to assess function layer-by-layer along the visual pathway. The clinical value of these for early detection glaucoma will be discussed. The pattern electroretinogram (PERG), a direct functional indicator of retinal ganglion cell function, is markedly affected by glaucoma, and in longitudinal studies the PERG correctly indicated eyes at risk before manifest glaucoma occurred. Consequently, this report will concentrate on the PERG. Less proven, but promising measures like the “photopic negative response”, the motion visually evoked potential (VEP) and the multifocal VEP will also be touched upon.

KEY WORDS: IOP, Diagnosis, Glaucoma, Pattern electroretinogram (PERG), Visual electrophysiology, Multifocal VEP

Why early diagnosis?

While elevated intraocular pressure (IOP) is a major risk factor for developing glaucoma, only about 1% of patients with an IOP of 25 mmHg actually develop manifest glaucoma each year. Prospective studies have reported incidences of 0.4% to 17.4% [1-6]. This wide range is largely due to differing study populations with different risk factors or degrees of pressure elevation. Since a sizeable proportion (25-30%) of the ganglion cells is already lost when visual field losses are apparent [7, 8], the aim of early detection is to identify those patients with elevated IOP who have early stage glaucoma damage before visual field changes occur.

The magnocellular vs parvocellular pathway

Research on early diagnosis has been dominated for more than a decade by the “magnocellular paradigm”, starting with Quigley’s observation [9]: “in early glaucoma ... [there is] preferential damage to large nerve fibers”. Previous sub-divisions had been based on psychophysical intricacies [10] but Quigley’s observation came at a time when division of the visual system into (at least) two major sub-systems was rekindled [11, 12]. The two major sub-systems that Quigley considered were the magnocellular stream (with large axons, making it the candidate for Quigley’s observation) and the parvocellular stream. This clear-cut hypothesis had two major consequences:

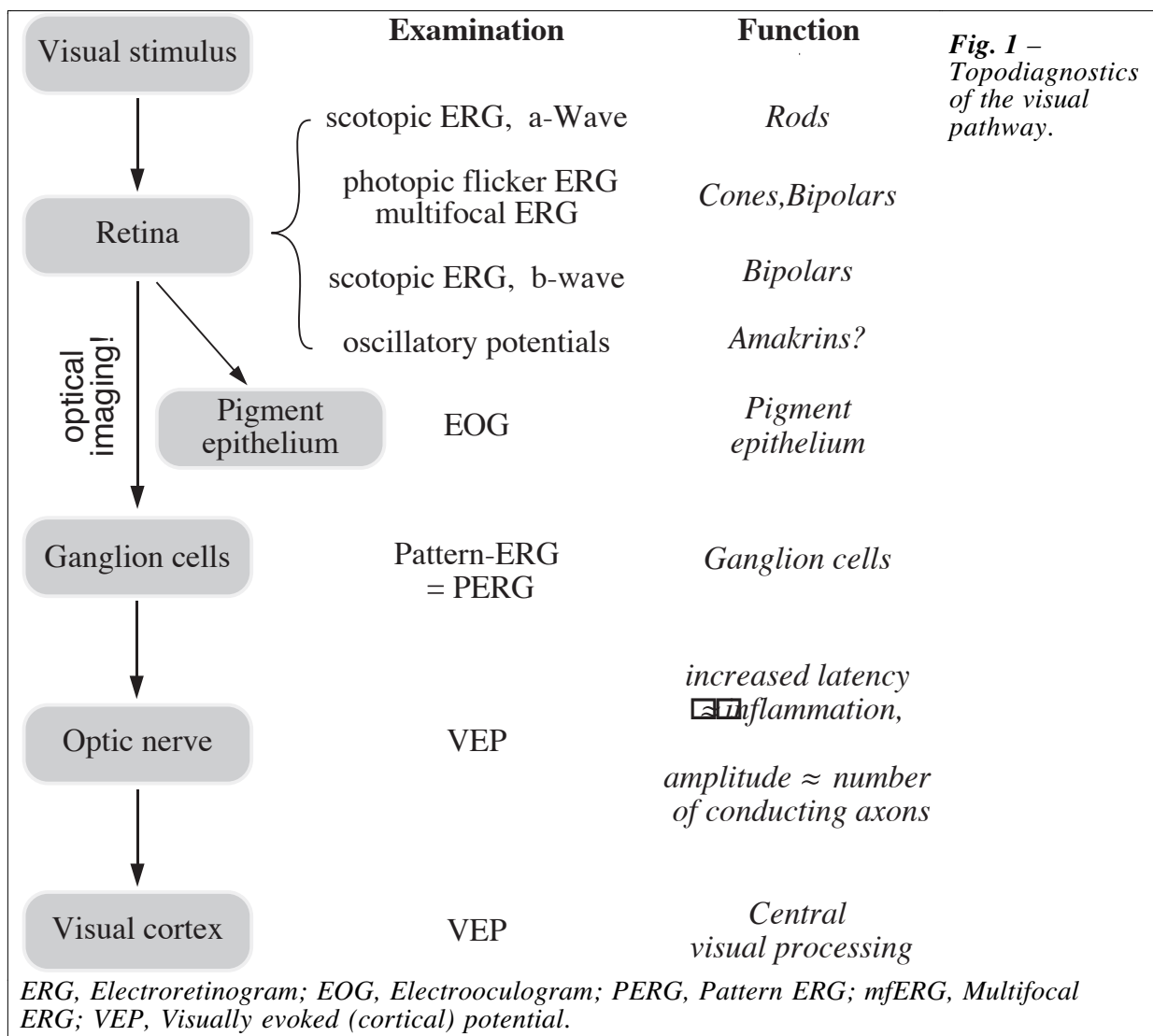
- It spurred basic scientists to challenge this simple view, find exceptions and limit its applicability.
- It led some applied researchers to oversimplified stimulus paradigms to selectively drive the magnocellular system.

For more than a decade, research on early diagnosis was dominated by the “magnocellular damage theory”. While this inspired interesting methodological developments, many researchers now feel that magnocellular damage in early glaucoma is only marginally greater – if at all – than parvocellular damage [13]. For instance, the well-known early blue deficits in glaucoma [14] cannot readily be explained by a magnocellular mechanism. More recent hypotheses interpret glaucoma damage in terms of redundant or non-redundant systems, where the parvocellular pathway is viewed as redundant and the magnocellular and the koniocellular (blue–yellow channel) pathways are viewed as non-redundant. However, these aspects are not covered in this report which concentrates on electrophysiological techniques organized according to their potential clinical value for early detection of glaucoma. In some cases, more work is required to validate the views presented here.

Electrophysiology

Visual electrophysiology commands a broad arsenal (Figure 1). For each of the various processing stages passed by a visual input, there is an investigative technique to assess functional integrity. When the pathophysiology of a disease process is known, Figure 1 shows where to expect, or look for, functional deficits.

Glaucoma starts when communication between the ganglion cell terminals 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. When we consider this pathophysiology, it is not surprising that many of the techniques used in visual electrophysiology have had little success.



Techniques that have been unsuccessful in early diagnosis of glaucoma

It is currently unclear whether only the ganglion cells are affected in optic atrophy. Van Buren [15] observed a “cystic degeneration in the inner nuclear layer” after a lesion of the chiasm. Later reports [16, 17] suggested that atrophy of the retinal ganglion cells affects amacrine or bipolar cells trans-synaptically.

Despite evidence that the bipolars may be affected in glaucoma [17], the electroretinogram (ERG), an indicator of rod- (a-wave), bipolar- (b-wave) and cone-function (flicker-ERG), remains nearly normal even in eyes blind from the condition [18] (Fig. 2). The same applies to the multifocal ERG (mfERG), which is a new technique [19, 20] that has been recently applied to glaucoma, but with a negative result [21].

The electrooculogram (EOG) is a slow potential change, indicating metabolic transport through Bruch’s membrane on demands by the photoreceptor. Consequently, there are no reliable reports on EOG application in glaucoma.

Techniques yet unproven in the early diagnosis of glaucoma

A number of exciting new electrophysiological methods have been advanced. Only some of these can be briefly touched upon here.

Recent animal-based research suggests that a component of the ERG, the “photopic negative response”, may be a sensitive indicator of glaucoma damage [22-24].

The multifocal VEP [25] provides a spatially-resolved VEP and can provide an objective functional correlate of conventional visual field measures. One group found a high correlation between field defects and the multifocal VEP [26], while others stress the high interindividual variability, rendering only interocular comparisons valid [27].

The motion VEP [28-30] appeared promising because motion perception is largely mediated by the magnocellular pathway (at least for low contrast [31]). Indeed, moderate impairment of motion perception in glaucoma was seen psychophysically [32]. More recently, the Korth group assessed motion VEPs in glaucoma. They observed a strong glaucoma-effect on amplitude, while little on latency of the VEP [33].

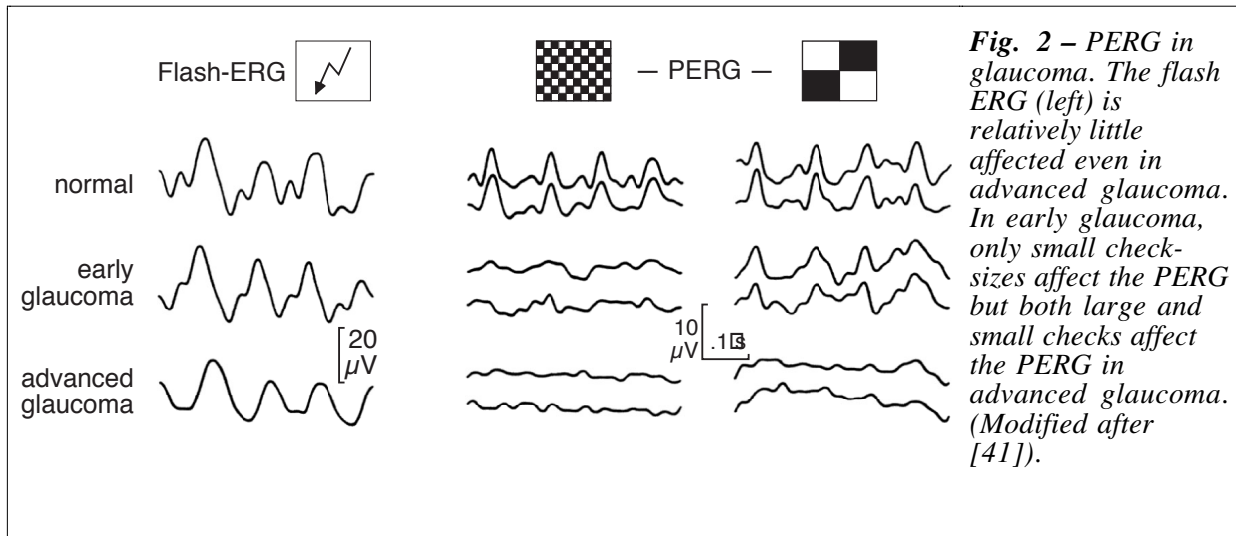
All of these promising techniques are awaiting prospective longitudinal studies to confirm their promise for early diagnosis.

Techniques proven effective in the early diagnosis of glaucoma – PERG

Principles of the PERG

The pattern ERG (PERG) is a direct indicator of ganglion cell function 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 standard [34].

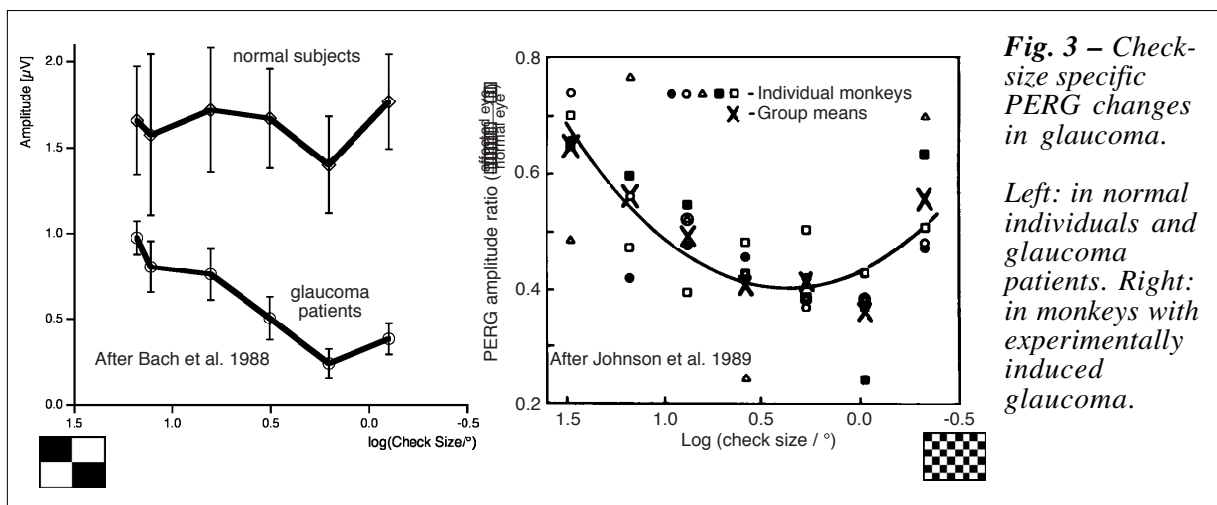
As stimulus, a checkerboard pattern is used, which reverses its local luminance while keeping average luminance constant. Thus, the ERG signals cancel out and non-linearities remain that have been shown to originate in the ganglion cells [18, 35, 36]. Retinal potentials are detected with a corneal electrode. Various types of electrode may be used, such as gold foil [37] or DTL [38, 39]. However, it is important that the electrode does not degrade the optical imaging on the retina, as reduced retinal contrast leads to marked reduction of the PERG. With an appropriate technique, a high stability and reproducibility can be obtained (inter-session coefficient of variation of approximately 10% [40]). The frequency of the checkerboard reversal determines whether the transient response (< 4 rev/s) or the steady-state response (≥ 8 rev/s) is evoked.



PERG in glaucoma

Figure 2 shows recordings from a normal individual, a patient with early glaucoma, and a patient with advanced glaucoma [41]. In the left column, ERG responses to a flash stimulus show little change in glaucoma. In contrast, the PERG to small check sizes (0.8°, centre 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.

Figure 3 shows the check-size specific effect in further detail. On the left are findings in 15 glaucoma eyes, while on the right are results from experiments with experimentally induced glaucoma in monkeys [42]. Both experiments show that the PERG to large checks is relatively little affected in glaucoma, with increasing effect with decreasing checksize. There is also an indication that with very small checks (<0.5°) the glaucoma effects become smaller again. These differential effects of check size have useful implications when using the PERG in early diagnosis of glaucoma.

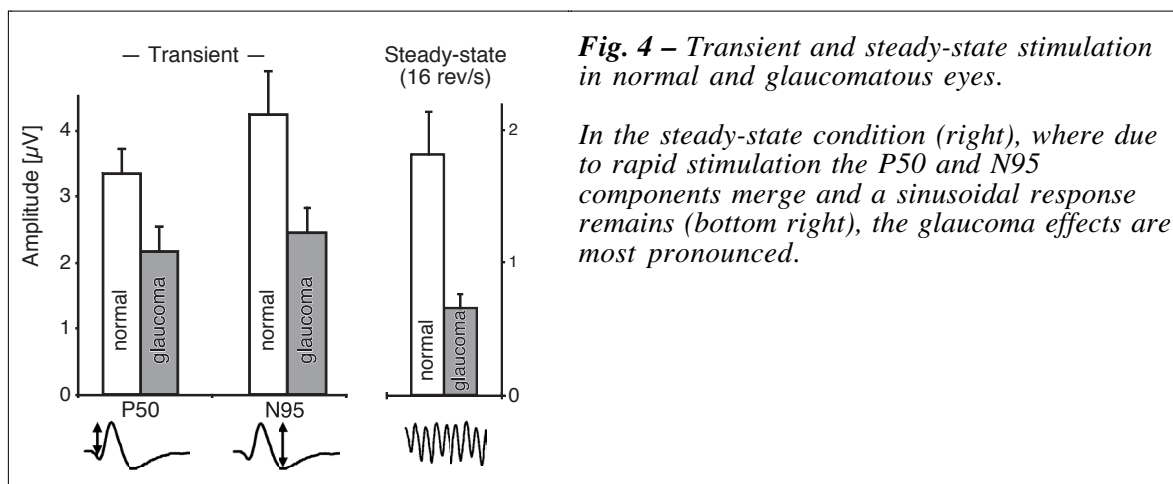


PERG in glaucoma: Transient vs steady-state stimulus conditions

When the transient PERG to relatively slow reversing patterns is recorded, a positive (P50) and negative (N95) component can be discerned. These may be affected differently in retinal and optic nerve diseases [43]. However, in glaucoma, both components appear equally affected.

In a group of eight normal control eyes and 23 eyes of 12 glaucoma patients, the PERG to transient stimulation and to steady-state stimulation were compared. Figure 4 (unpublished results) shows that in the transient response, both the P50 and the N95 component were affected to a similar degree in glaucoma. In contrast, the steady-state response is relatively much more affected by glaucoma (right of Fig. 4). Furthermore, rapid stimulation at 16 rev/s showed a much more pronounced amplitude reduction than did transient stimulation, when compared in the same glaucoma patients [44]. At reversal rates higher than 18 rev/s returns are diminishing for normal/glaucoma discrimination in the PERG [45]. These frequency-dependent effects correspond with psychophysical work that showed more glaucomatous effects at higher temporal frequencies [46, 47].

Altogether, this evidence suggests that PERG recording at medium-high temporal frequencies is most efficacious to detect incipient glaucoma damage.



“Freiburg“ PERG paradigm

While the group differences in the PERG amplitude between normal controls and glaucoma patients are easily highly significant, it is still questionable whether a useful risk assessment can be performed on an individual basis. To tackle this problem, we arrived at the following paradigm.

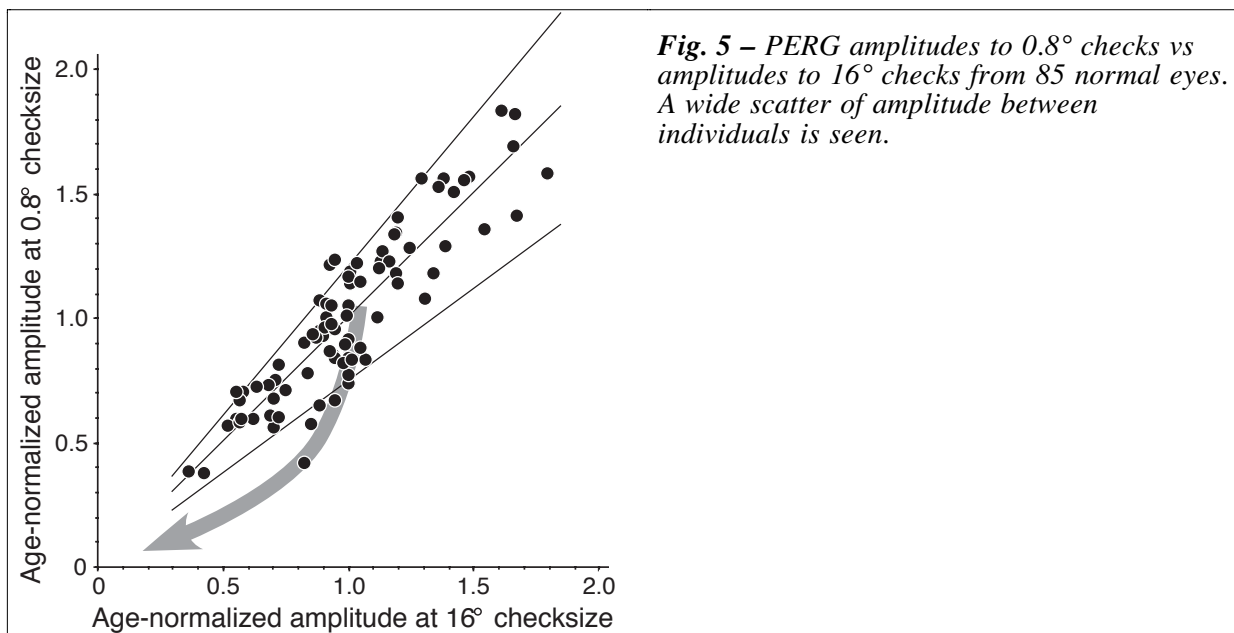
First, steady-state stimulation of 16 rev/s is employed. This frequency is believed to be in the optimum range, because there is less glaucoma sensitivity at lower (e.g. 8 rev/s) and higher rates (e.g. 16 rev/s) [44, 45], probably because of decreasing signal/noise ratio. The exact reversal rate depends also on the equipment, as aliasing by the frame rate of the stimulus monitor must be avoided [48].

Second, we combine two check sizes, 0.8° and 16°. This reduces the effect of interindividual variability – PERG amplitude varies by a factor of three between individuals. Recalling Figure 3,

note that the PERG to 0.8° checks are strongly affected by glaucoma, whereas the PERG to 16° checks are not. Since the interindividual variability is multiplicative, such that an individual with a large 0.8°-PERG will also have a large 16°-PERG, it makes sense to compute the ratio:

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

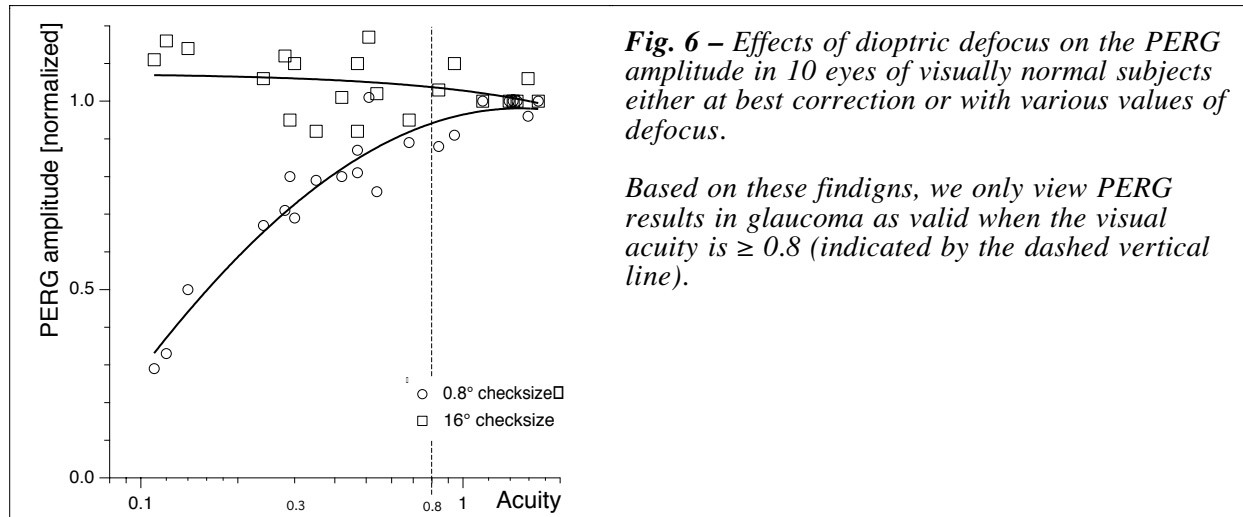
In Figure 5, the scatter of a normal control population is seen (data extended from [49]). There is a high correlation between the amplitudes to 0.8° and 16° check-size. In glaucoma, initially the 0.8°-response is reduced, then later the 16°-response. Consequently, a (treatment-resistant) glaucoma eye will presumably follow the hypothetical curve indicated by the curved arrow in Figure 5. A constant PERG-ratio corresponds to an oblique straight line in this figure. For individual diagnosis, the lines indicate the lower 5% confidence interval for the PERG-ratio, the 45°-line, and the upper 95% confidence interval. PERGs from individual eyes that fall below the lower confidence line are at risk of developing glaucoma.



A problem: reduced acuity

Any degradation of retinal imaging (e.g. cataract or defocus) leads to amplitude reduction [50]. Dioptric defocus is the more problematic case here, since it affects the PERG to 0.8° checks and not the PERG to 16° checks [51], changing the PERG-ratio in the same manner as glaucoma would (Fig. 6). PERG was recorded in 10 eyes of visually normal eyes either at best correction or with various values of defocus, covering an acuity range from 0.1 to 1.6. Increasing defocus markedly reduces PERG amplitude when 0.8° checks are employed, but has no significant effect when a 16° check size is employed (Fig. 6). Wide-angle scattering, as occurs with cataracts, also affects the 16°-response, leading to less marked effects on the PERG-ratio. The effects are easily understood when the low-pass nature of defocus and the PERG's linear contrast-amplitude characteristic are taken into account [52, 53].

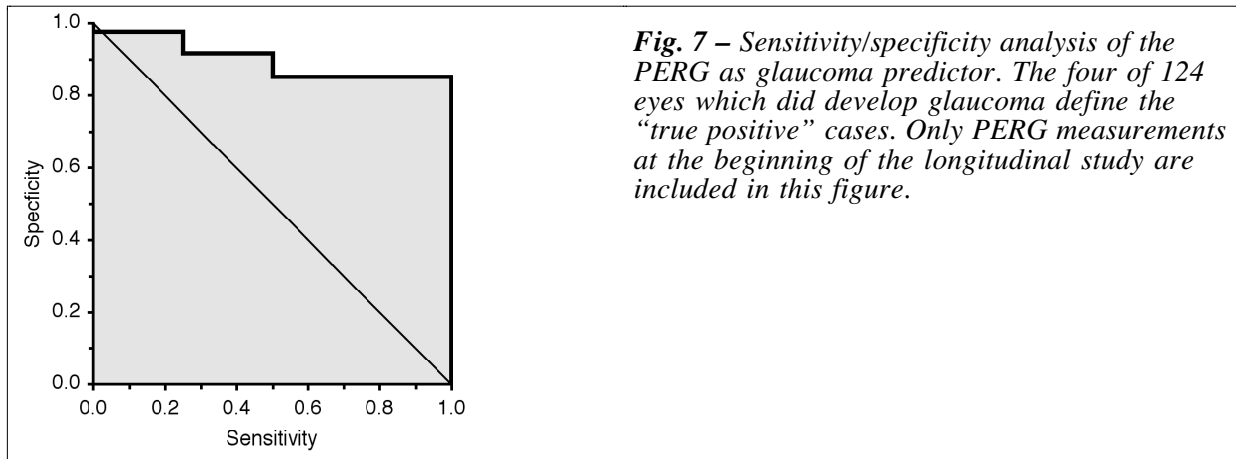
To avoid false positive results, we perform PERG-glaucoma testing only on eyes with a visual acuity ≥ 0.8 , tested at the PERG-stimulus distance of 57 cm with a semi-automatic procedure [54]. While optical correction can be optimized, unfortunately many glaucoma patients have media opacities, thus precluding PERG testing.



PERG in OHT – longitudinal studies

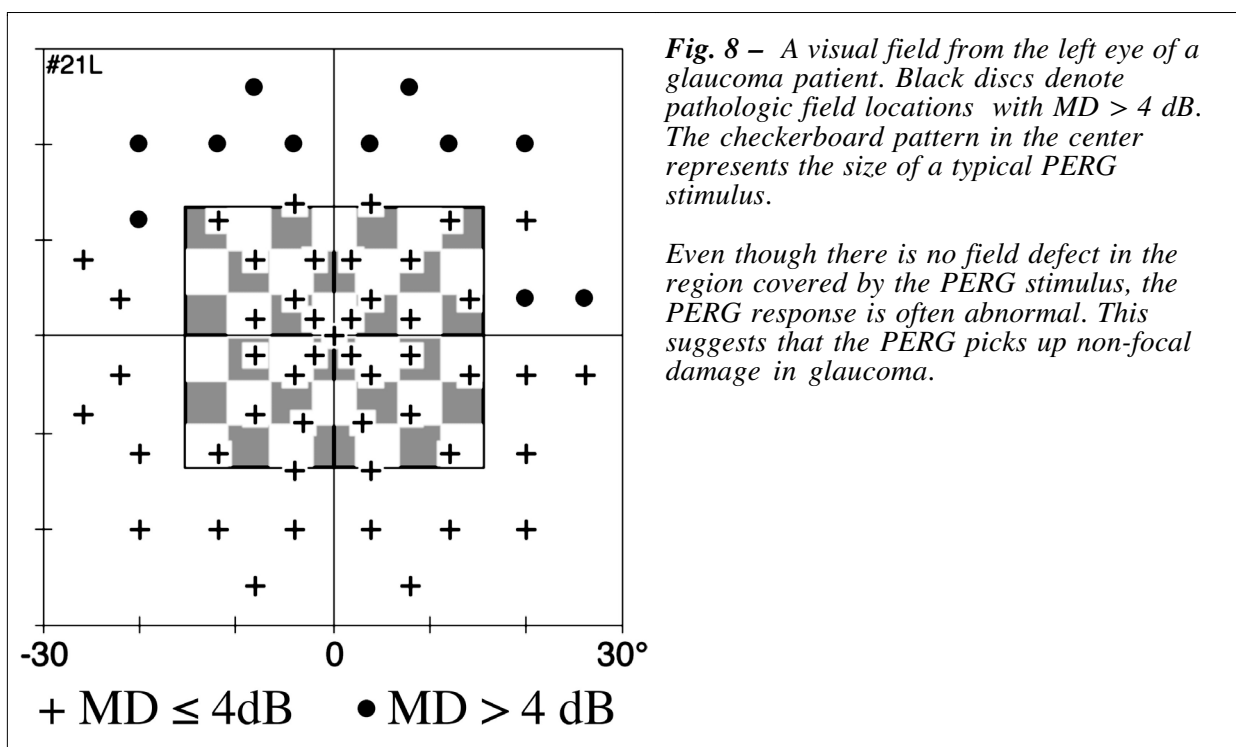
In order to prove the utility of the PERG as an early glaucoma indicator, longitudinal studies have been performed to test whether the PERG identifies eyes with elevated IOP that later develop manifest glaucoma. There is a relative scarcity of such studies, due largely to the need of long-term investment of sizeable resources 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 years [55]. 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 study [56], we recorded the history of 124 eyes of 67 patients with initial IOP > 24 mmHg and no apparent visual field damage for up to 8 years (mean follow-up time 5.9 years). Over this time, four eyes of four patients developed manifest glaucoma. This low incidence was expected, but made it difficult to assess the predictive value of the PERG. By varying the pathology-threshold of the PERG-ratio (defined above), we compared the sensitivity and specificity of the technique. The results of the sensitivity/specificity analysis (also known as receiver operating characteristic [ROC] analysis) are shown in Figure 7. For a sensitivity of 100%, there was a high specificity of 85%. While this may be a chance high value (only four true positives), the data suggest that the PERG is of value in defining eyes that are at higher risk of developing manifest glaucoma.



PERG may reveal “panretinal ganglion cell damage”

In hindsight it was 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 cells [49], 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 Figure 8. In 13 of 18 such eyes (from 16 patients) with a normal visual field in the stimulated area, we obtained a pathologic PERG [57]. This suggests that the PERG picks up a “panretinal” damage mechanism, which affects the ganglion cells before reliable field damage is observed.



Conclusion

The PERG can be useful in early diagnosis of glaucoma. With appropriate recording techniques and paradigms, it can identify eyes at risk before manifest field damage with a specificity of 85%. It should be recognised 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 the best documented electrophysiological technique for detecting early glaucoma damage. It should help in identifying those patients with elevated IOP in whom glaucoma damage is incipient before visual field changes occur.

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