Chapter 5

Electrophysiology in the Diagnosis of Glaucoma

5

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Core Messages

- Among the electrophysiological procedures in ophthalmology, pattern ERG (PERG) recordings are the most useful test for an early detection of glaucoma at this time.
- PERGs are recorded in response to contrast-reversing checkerboard patterns. In early stages of glaucoma steady-state PERGs to checkerboard patterns with small check sizes (around 0.8°) are preferentially reduced in amplitude.
- Due to a sizeable interindividual amplitude variability, this amplitude change in glaucoma is best assessed by a PERG ratio, where the PERG amplitude to small checks is normalized by the PERG amplitude to large checks in the same patient.
- In a prospective study the PERG ratio was shown to identify eyes at risk before manifest field damage; thus, PERG recordings under appropriate recording conditions may help to identify patients with elevated IOP in whom glaucoma damage is incipient before visual field changes occur.
- A selective stimulation of ganglion cells in the magnocellular stream of the visual system seems less promising, as earlier hypotheses about a preferential damage of magnocellular ganglion cells in earlier stages of glaucoma could not be validated.
- Recently, new methods to study the effect of glaucomatous ganglion cell damage on cortical potentials (VEPs) have been presented that may improve the early detection (S-cone VEP) and the follow-up of glaucoma (mfVEP) in the future.

5.1 Introduction

5.1.1 Glaucomatous Damage of Ganglion Cells

Ganglion cells are inner retinal neurons that receive inputs from bipolar and amacrine cells and that subserve the transmission of visual information via the optic nerve to the visual cortex. It is known that ganglion cell death in glaucoma is a multi-factorial mechanism of apoptosis [20]; however, it is still unknown how the different factors (e.g., mechanical compression by elevated intraocular pressure, vascular dysfunction, or neurotrophic deprivation) interact in the manifestation of glaucomatous atrophy of ganglion cells. Significant loss of ganglion cells will inevitably result in visual disability; however, there is built-in redundancy within the visual system, so that a larger number of neurons can be lost without becoming manifest on standard tests of visual function. Approximately 25–30% of the ganglion cell fibers can be lost before significant visual field defects are observed [52]; thus, an early detection of glaucoma is complicated by the fact that no visual impairment is perceived by the patients in this early stage.

The search for an early indicator for glaucomatous damage to the ganglion cells was inspired for several years by the dichotomy of magnocellular and parvocellular streams within the visual system [61, 62]. These two sub-systems can be activated selectively by appropriate visual stimuli, e.g., motion stimuli are processed by the magnocellular system, while isoluminant stimuli with a color contrast but no luminance contrast are processed by the parvocellular system [61, 62]. These sub-divisions of the visual system became relevant for glaucoma diagnosis after Quigley et al. [83] described that large nerve fibers of the magnocellular stream are preferentially damaged in early glaucoma. For more than a decade,

research on early diagnosis was dominated by this „magnocellular damage paradigm." Meanwhile, this paradigm had been challenged by new experimental data and there is evidence that magnocellular damage in early glaucoma is only marginally greater – if at all – than parvocellular damage. Crawford et al. [26] quantified the effect of experimental glaucoma in monkeys by the reduction in metabolic drive as indicated by cytochrome oxidase histochemistry. The detrimental effect of experimental glaucoma did not appear to be any greater for the magnocellular system than for the parvocellular system in the LGN or in the visual cortex. Yücel et al. [103] quantified LGN nerve fiber loss in a primate glaucoma model and reported that neurons in the parvocellular layers undergo even more shrinkage than neurons in magnocellular layers. Recently, Spry et al. [88] compared a variety of psychophysical tests to evaluate ganglion cell loss in early glaucoma. They stress the importance of ganglion cell sub-populations with lower levels of redundancy for the explanation of early ganglion cell loss in glaucoma. Moreover, the deficits in blue–yellow color perception as exploited by short-wavelength perimetry in early glaucoma [84] cannot be explained with a preferential damage of the „color-blind" magnocellular subsystem.

Summary for the Clinician

- Approximately 25–30% of the ganglion cell fibers can be lost before significant visual field defects are observed.
- A „preferential magnocellular damage" can no longer be used as a model for the pathological changes in early glaucoma.

5.1.2 The Importance of Early Detection of Glaucoma

Elevated intraocular pressure (IOP) is a well-known risk factor for glaucoma that had once been used as a synonym for glaucoma but had been out of focus during the past decade due to a concentration on molecular mechanisms, genetical risk factors, and neuroprotective strategies in basic research. Recently, two clinical studies have demonstrated the importance of an elevated IOP on the progression of glaucoma.

The Early Manifest Glaucoma Trial (EMGT) was designed to determine the efficacy of IOP lowering by a combination of betaxolol therapy and argon laser trabeculoplasty in subjects with documented glaucomatous damage [35]. The EMGT confirmed the role of IOP as a major risk factor and showed that each mmHg of IOP lowering was associated with an approximate 10% decrease in risk of glaucoma progression. The Ocular Hypertension Treatment Study (OHTS) tested patients with an elevated IOP between 24 and 32 mmHg in at least one eye, but normal visual fields and normal optic nerves [51]. Patients with IOP lowering of 20% below baseline and less than 24 mmHg were less likely to convert to glaucoma over 5 years (4.4 %) than patients without treatment (9.5%); thus, an early identification of patients at risk is essential to delay glaucoma progression.

For a patient with an elevated IOP of 25 mmHg the risk to develop manifest glaucoma is only about 1% per year; however, a comparison of different studies shows a large variation between 0.4% and 17.4% for this percentage, probably due to differing study populations with different risk factors or degrees of pressure elevation [4, 33, 48, 78, 99]. One important confounding factor for a closer correlation of IOP and glaucomatous progression is the central corneal thickness, which can affect IOP measurement by Goldmann applanation tonometry. The Ocular Hypertension Treatment Study (OHTS) verified within their pool of 1636 subjects that an increased central corneal thickness was more common among patients with ocular hypertension (OHT) [23]. The OHTS data suggest that many OHT patients may have little more than thickened corneas that result in their misclassification on the basis of Goldmann tonometry. This finding demonstrates the importance of identifying glaucomatous damage to the ganglion cells at an early stage, before irreversible retinal damage and visual field loss has occurred, while sparing patients who have „just" an elevated IOP or a thickened cornea. There exist well-developed psychophysical and morphological techniques

Table 5.1 Electrophysiological techniques for glaucoma management

Method	Abbreviation	Useful in glaucoma	Comment
Electroretinogram	ERG	Standard paradigm: No PhNR: Possibly	Useful in detecting retinal diseases
Electrooculogram	EOG	No	Function of the pigment epithelium
Multifocal ERG	mfERG	Standard paradigm: No Specialized paradigms: Possibly	Useful in detecting localized retinal damage
Pattern ERG	PERG	Yes	Early indicator of glaucoma damage
Visual evoked potential	VEP	Standard paradigm: No S-cone VEP: Possibly	Function of the entire visual pathway, dominated by the center
Multifocal VEP	mfVEP	Possibly	Promise of objective perimetry

to monitor the course of glaucoma to assess therapeutic efficacy, but early detection could well profit from electrophysiological techniques, as will be seen.

Summary for the Clinician

- Recently, two clinical studies have demonstrated the importance of an elevated intraocular pressure on the progression of glaucoma.
- The large proportion of patients with ocular hypertension that will never develop glaucoma demonstrates the need to identify those eyes at risk before irreversible retinal damage and visual field loss has occurred.

5.1.3 Electrophysiological Procedures in Ophthalmology

Electrophysiological procedures allow a recording of surface potentials that are generated by the neurons of the visual system in response to flash and pattern stimuli. Compared with imaging techniques in ophthalmology (e.g., optical coherence tomography, fluorescein angiography, or ultrasound sonography), the electrophysiological methods are *functional* tests, as the evoked surface potentials are by-products of signal processing within the visual pathway. Compared with psychophysical procedures in ophthalmology (e.g., perimetry, visual acuity testing, or color vision testing) the electrophysiological methods allow an objective *localization* of functional deficits, as the type of the recording enhances the contribution of specific neurons along the visual pathway (e.g., photoreceptors, bipolar cells, ganglion cells, or optic nerve). During past decades a sophisticated framework of electrophysiological test procedures has been put forth for separate functional testing of the different neural structures along the visual pathway (Table 5.1). Although most of these procedures are not suited to detect glaucomatous damage of retinal ganglion cells (Table 5.1, third column), they play an important role in the differential diagnosis to exclude other disorders of the visual system (Table 5.1).

- The scotopic and photopic flash-ERG is driven by photoreceptors and bipolar cells and is used to diagnose diseases of the outer retina such as retinitis pigmentosa [66].
- The electro-oculogram (EOG) measures changes in the standing potential of the eye in a sequence of dark and light adaptation intervals and is a functional test of the retinal pigment epithelium, e.g., in Best's maculopathy [68].

- The pattern ERG (PERG) reflects ganglion cell activity and is an important tool to study pathological changes of the inner retina such as glaucoma [8].
- The visual evoked potential (VEP) is recorded over the occipital pole of the head and is used for functional testing of the optic nerve and the first processing steps within the visual cortex [73].

One of the most fascinating developments in the field of ophthalmological electrophysiology during the past decade was the introduction of multifocal recordings by Sutter [90] and Sutter and Tran [91]. This method allows a simultaneous recording of local ERG, PERG, and VEP responses from more than 100 regions within the visual field [67]. As multifocal recordings bridge the gap between standard electrophysiological procedures and perimetry, this method is often denoted as „objective perimetry".

However, neural responses to any stimulus are processed by all stages of the visual pathway from the photoreceptors to the visual cortex. This has four important implications for the electrophysiological diagnosis of glaucoma.

- The isolation of inner and outer retinal ERG contributions by applying flash and pattern stimuli is less complete than might be expected from the simplifying classification mentioned above, e.g., Viswanathan et al. [97] blocked the action potentials of retinal ganglion and amacrine cells and demonstrated that the photopic negative response (PhNR), a late component in the photopic fullfield flash-ERG around 90 ms, is generated by the inner retina. By applying this promising new PhNR technique, several groups found a reduction of the PhNR component in glaucoma patients [25, 27, 29, 98]. Since the currently available data on PhNR from different laboratories are somewhat conflicting, we do not cover the PhNR here.
- The PERG responses may be reduced as a consequence of photoreceptor or bipolar dysfunction, when ganglion cells do not receive an appropriate input; thus, the integrity of the earlier processing steps must be validated, e.g., by scotopic and photopic flash-ERG recordings or by multifocal ERG recordings (Table 1), before an abnormal PERG response can be traced back to a specific ganglion cell dysfunction.
- No pattern stimulus can be reversed in contrast without an associated local luminance modulation; thus, responses from luminance mechanisms within the outer retina may potentially be superimposed on pattern specific responses. This superposition of inner and outer retinal contributions in the processing of pattern stimuli led to controversies about the neural origin of the PERG.
- Ganglion cell activity generates the neural input for further processing along the visual pathway; thus, glaucomatous damage of ganglion cells may have a significant impact on VEP or multifocal VEP responses (Table 5.1). The advantage of using the VEP for glaucoma detection is that – in contrast to PERG recordings – no signal intrusion from luminance mechanisms of photoreceptors and bipolar cells is expected in cortical recordings; however, active VEP electrodes are placed over the occipital cortex in a larger distance to the pathological site of glaucoma-caused damage when compared with PERG electrodes.

In the following sections we review the current contributions of the different electrophysiological recording procedures to the early detection of glaucoma. We focus mainly on PERG data, where a glaucomatous damage of ganglion cells can be observed most directly. The reminder of the chapter summarizes glaucomatous changes to VEP and multifocal VEP (mfVEP) recordings.

Summary for the Clinician

- Ganglion cell function can be observed in pattern (PERG) recordings.
- Multifocal recordings bridge the gap between standard electrophysiological procedures and perimetry.

5.2 Early Detection of Glaucoma Using PERG Recordings

5.2.1 PERG Recordings

The PERG is recorded in response to contrast-reversing checkerboard patterns where the mean luminance is constant in time. The retinal potentials are recorded with corneal electrodes. Various types of electrodes may be used, such as gold

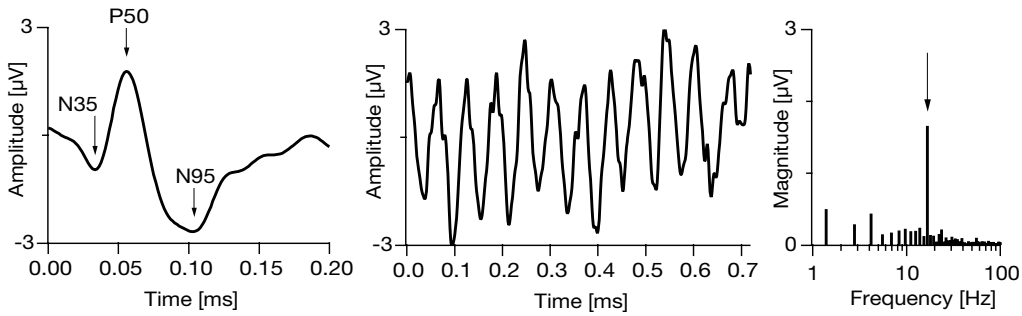

Fig. 5.1 Pattern ERG (PERG) waveform. **a** A transient PERG is obtained at slow stimulation rates. The waveform is characterized by a small negative component at approximately 35 ms (N35), followed by a larger positive component between 45 and 60 ms (P50) and a larger negative component at a 90–100 ms (N95). **b** At faster stimulation rates the so-called steady-state PERG is evoked. The waveform becomes roughly sinusoidal and Fourier analysis is required to determine the amplitude (right).

foil electrodes [1] or conductive fiber electrodes, like the DTL electrode [28]; however, it is important that the electrode does not degrade the optical image on the retina, as reduced retinal contrast leads to marked reduction of the PERG [36, 104]. With an appropriate technique, a high stability and reproducibility with an inter-session coefficient of variation down to 10% can be obtained [74]. A more detailed description of the PERG recording procedure can be found in the ISCEV standard [8].

With low temporal frequencies of less than 6 reversals per second (rps) a transient PERG is obtained (Fig. 5.1a). The waveform is characterized by a small negative component at approximately 35 ms (N35), followed by a larger positive component between 45 and 60 ms (P50) and a larger negative component at about 90–100 ms (N95). At higher temporal frequencies above 10 rps the successive waveforms overlap and the so-called steady-state PERG is evoked (Fig. 5.1b). The waveform becomes roughly sinusoidal and Fourier analysis is required to determine the amplitude and temporal phase shift relative to the stimulus [11].

5.2.2 Neural Origin of PERG Responses

The search for an electrophysiological indicator of glaucomatous damage is related to finding stimulus conditions that isolate signals from retinal ganglion cells, if possible without any intrusions from photoreceptor or bipolar cell activity. Meanwhile it has been validated that PERG recordings approach this optimum closely. The way in which this validation process was performed is an example for the cross-fertilization of basic research and clinical application that can be found in ophthalmological electrophysiology. The clinical diagnosis benefits from the development of new testing procedures, whereas the interpretation of the evoked responses has been clarified by specific changes under well-defined pathological conditions.

As each pattern reversal of a checkerboard is associated with local luminance increments and decrements, the outer retina adds to the activity of the inner retina during pattern stimulation, as was demonstrated by current source-density studies in cats and primates [17, 86, 106]. If the ERG would be a linear function of the stimulus intensity, the responses to luminance increments and decrements during a pattern stimulation would be exact mirror images and would cancel out; however, the ERG also contains nonlinear components [16, 24]. In addition, the PERG may contain lateral interaction components as bipolar cells, amacrine cells, and ganglion cells collect contrast information within their receptive field with center-surround antagonistic organization [57, 71].

The superposition of luminance specific and lateral interaction specific PERG components led to intense and controversial discussions about

the neural origin of the PERG. Spekreijse [87] found that the cortical VEP responses clearly depended on spatial contrast, whereas the retinal PERG responses seemed to be dominated by the luminance properties of the stimuli. The Arden group challenged this view and showed that a pattern specific subcomponent can be identified by applying extensive computer averaging and artifact rejection [2, 3].

A more pragmatic way to clarify whether the PERG is a veridical ganglion cell response is to monitor full-field flash-ERG changes and PERG changes after transection of the optic nerve. Maffei and Fiorentini [64], and Maffei and coworkers [65], demonstrated in cat and monkey that the PERG was progressively reduced at a rate consistent with ganglion cell degeneration, whereas the full-field flash ERG remained unchanged; however, differing results were found in pigeon, where a preservation of the P50 component of the PERG response was observed after transection of the optic nerve [21, 81]. In humans, only few PERG data of patients were reported where the completeness of a traumatic or surgical optic nerve section could be verified. Harrison et al. [34] reported one such case and found that the PERG response was reduced but not extinguished. In patients with optic nerve atrophy the degree of degeneration is difficult to quantify and the results of corresponding PERG studies were contradictory [2, 7, 30, 72, 85]. The most comprehensive reports on PERG abnormalities in patients with optic nerve diseases have been published by Holder [38–40]. Holder concluded that the N95 component of the transient PERG is generated by ganglion cells, whereas the P50 component reflects a mixture of inner and outer retinal contributions [39].

Summary for the Clinician

- Each pattern stimulus activates both inner and outer retinal neurons.
- Due to a close interaction of basic research and clinical application, it could be validated that PERG responses are generated by ganglion cells.

5.2.3 PERG Changes in Glaucoma

5.2.3.1 Historical Review

The first paper to report PERG recordings in a glaucoma patient was published by May et al. in 1982 [70]. In 1983 two papers appeared, one from Bobak et al. [22] and the first of Wanger and Persson's seminal work with 11 patients [101]. This was the starting point for a continuous stream of studies on PERG changes in glaucoma and ocular hypertension [5, 9, 14, 19, 31, 58, 63, 75, 77, 79, 80, 82, 93, 100, 102]. All but one of these papers report PERG amplitude reduction in glaucoma without significant effects on latency. The one exception is a study by van den Berg et al. [96], 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 of a glaucomatous eye is very high, and PERG reduction seems to precede obvious visual field loss. It is likely, therefore, that in van den Berg's study [96] PERG amplitudes were also reduced in the reference eye, thus eliminating differences during interocular comparison and leaving the effect of glaucoma on PERG amplitudes undetected.

5.2.3.2 Check-Size Specific Reduction

PERG to large stimulus checks is spared in early glaucoma. This is illustrated in Fig. 5.2, where recordings from a normal individual, a patient with early glaucoma, and a patient with advanced glaucoma are depicted [9]. 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°, 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. 5.3 in further detail. On the left, there are findings from 15 glaucoma eyes [9], whereas

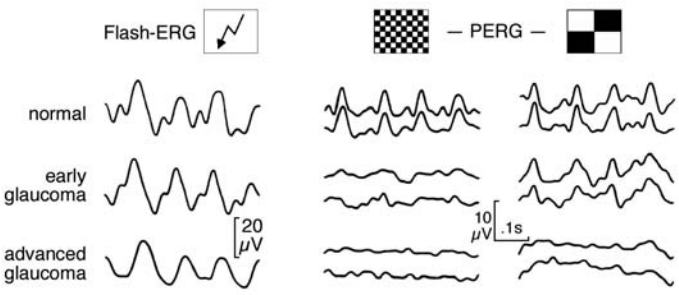

Fig. 5.2
ERG and PERG in glaucoma. The flash ERG (left column) is relatively little affected, even in advanced glaucoma. In early glaucoma (center row), there is a sizable reduction of the PERG to 0.8° checks and little reduction for 16° checks. In advanced glaucoma (bottom row), the PERG to any check size is reduced. (From [5], with permission, modified after [9])

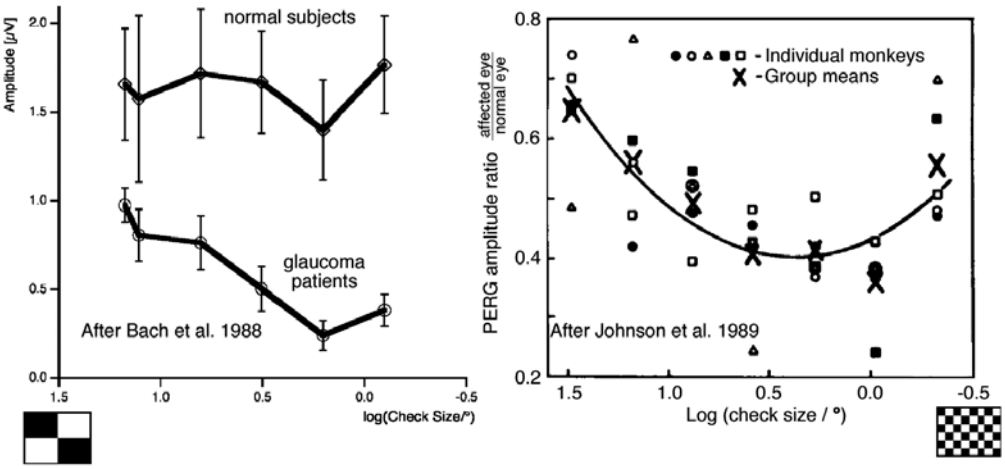

Fig. 5.3 Check-size-specific PERG changes in glaucoma. Left: human data from normal individuals and glaucoma patients (From [5], with permission, modified after [9]). Right: Non-human primates with experimentally induced glaucoma. (From [5], with permission, modified after [50])

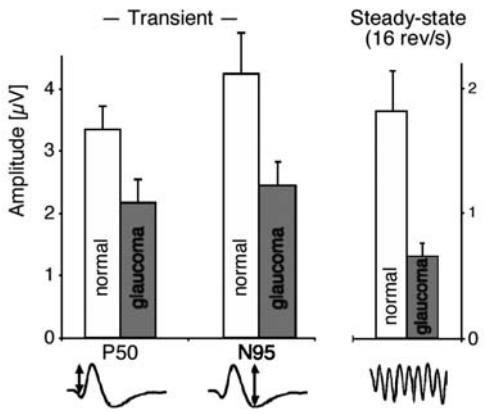

Fig. 5.4
P50 vs N95, transient vs steady-state stimulation with 0.8° checks in normal eyes (white bars) and glaucomatous eyes (gray bars). Transient stimulation (left two bar pairs) allows discrimination between the P50 and the N95 component. The relative effect of glaucoma is virtually identical. In steady-state stimulation at 16 rps (right bar pair) the relative glaucoma effect is most pronounced. (From [5], with permission)

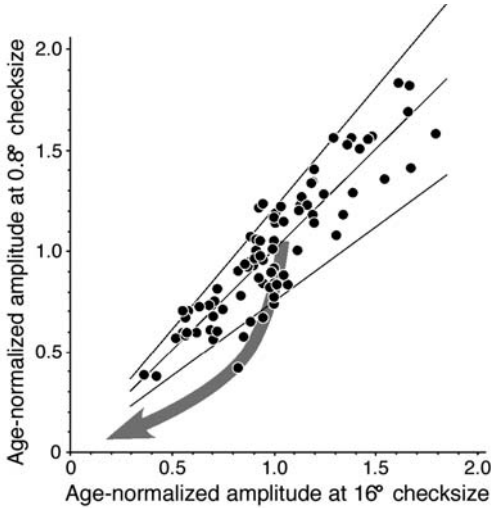

Fig. 5.5 PERG amplitudes to 0.8° checks vs amplitudes to 16° checks from 85 normal eyes. A wide scatter of amplitude between individuals is seen. The course of disease is likely to follow the arrow. (From [5], with permission)

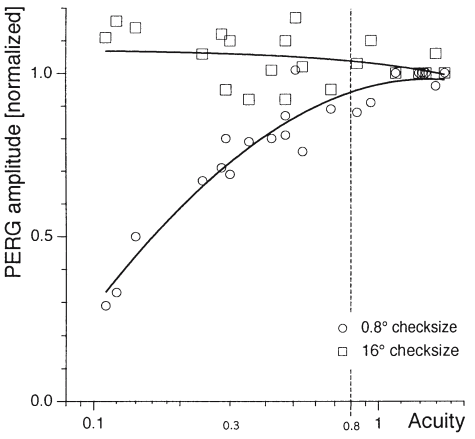

Fig. 5.6 Effects of dioptric defocus on the PERG amplitude in ten eyes of visually normal subjects either at best correction or with various values of defocus. Based on these findings, we only view PERG results in glaucoma as valid when the visual acuity is ≥ 0.8, as indicated by the dashed vertical line. (From [5], with permission)

results from experiments with experimentally induced glaucoma in monkeys are depicted on the right [50]. Both experiments show that the PERG to large checks is relatively little affected in early glaucoma, with increasing effect with decreasing check size. There is also an indication that with very small checks (< 0.5°) the glaucoma effects become smaller again as reported by Trick et al. [93]. These differential effects of check size have useful implications when using the PERG in early diagnosis of glaucoma, as is detailed in the following section.

5.2.3.3 P50 vs N95, Steady-State vs Transient Responses

In a group of 8 normal control eyes and 23 eyes of 12 glaucoma patients, the PERGs to transient stimulation and to steady-state stimulation were compared. Figure 5.4 shows that in the transient response, both 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, and 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 side of Fig. 5.4) [14]. When reversal rates become higher than 18 rev/s, returns are diminishing for normal/glaucoma discrimination in the PERG [37], probably because of decreasing signal-to-noise ratio.

These frequency-dependent effects have also been shown by Trick [92] and correspond well with psychophysical work that showed more glaucomatous effects at higher temporal frequencies [47, 59, 94]. Altogether, this evidence suggests that steady-state PERG recording at temporal frequencies between 10 and 20 rps is most efficacious to detect incipient glaucoma damage.

Summary for the Clinician

- Glaucomatous damage of ganglion cells leads to specific PERG changes (Table 5.1), mainly when PERGs are recorded with small check sizes (around 0.8°) and under rapid pattern-reversal conditions (“steady state”).

5.2.4 The "Freiburg" PERG Paradigm

5.2.4.1 Basic Paradigm

While the group differences in the PERG amplitude between normal controls and glaucoma patients are highly significant, it is still questionable whether a useful risk assessment can be performed on an individual basis. 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, because there is less glaucoma sensitivity at lower (e.g., 8 rev/s) and higher rates (e.g., 18 rev/s, probably because of decreasing signal/noise ratio, [14, 37]). The exact reversal rate also depends on the equipment, as aliasing by the frame rate of the stimulus monitor must be avoided [12].

Secondly, two check sizes, 0.8° and 16° were combined. This reduces the effect of interindividual variability (PERG amplitude varies by a factor of three between individuals). Recalling Fig. 5.3 we note that the PERGs to 0.8° checks are strongly affected by glaucoma, whereas the PERGs 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 as follows:

$$\text{PERG-ratio} = \frac{\text{PERG amplitude to 0.8° checks}}{\text{PERG amplitude to 16° checks}}$$

In Fig. 5.5 the scatter of a normal control population is seen (data extended from [7]). 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, an untreated or treatment-resistant glaucoma eye will likely follow the hypothetical curve indicated by the curved arrow in Fig. 5.5. A constant PERG ratio corresponds to the 45° line in Fig. 5.5. For individual diagnosis, the lower and upper lines indicate the 5 and 95% confidence interval for the PERG ratio, respectively. The PERGs from individual eyes that fall below the lower confidence line are at risk of developing glaucoma.

5.2.4.2 The Problem: Reduced Acuity

Any degradation of retinal imaging (e.g., cataract or defocus) leads to amplitude reduction [10]. 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° checks [9], thus changing the PERG ratio in the same manner as glaucoma would. This is illustrated in Fig. 5.6: 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 0.8° 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 easily understood when the low-pass nature of defocus and the PERG's linear contrast-amplitude characteristic are taken into account [36, 104].

To avoid false-positive results, the Freiburg group performs 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 [6]. While optical correction can be optimized, many glaucoma patients have beginning media opacities, thus precluding PERG testing.

5.2.4.3 PERG in OHT: Longitudinal Studies

In order to test 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, largely due to the need of long-term investment of sizeable resources and the loss of patients to follow-up. In an early study, the Freiburg group 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 1–3 years [79]. Initially, in 12 of these eyes the PERG was abnormal, and 5 of these eyes did develop glaucomatous field defects. In contrast, none of the eyes with initially normal PERG developed glaucomatous field defects.

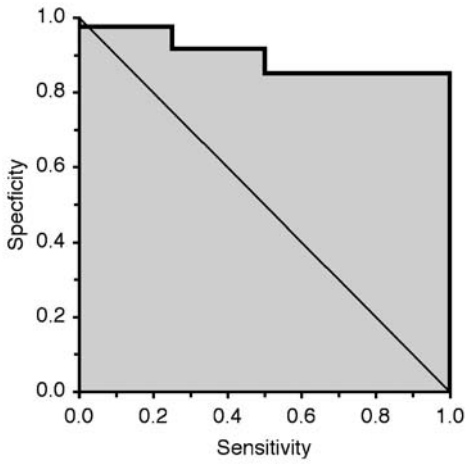

Fig. 5.7 Sensitivity/specificity analysis of the PERG as glaucoma predictor. The 4 of 124 eyes which did develop glaucoma define the "true-positive" cases. Only PERG measurements at the beginning of the longitudinal study are included in this figure. (From [5], with permission)

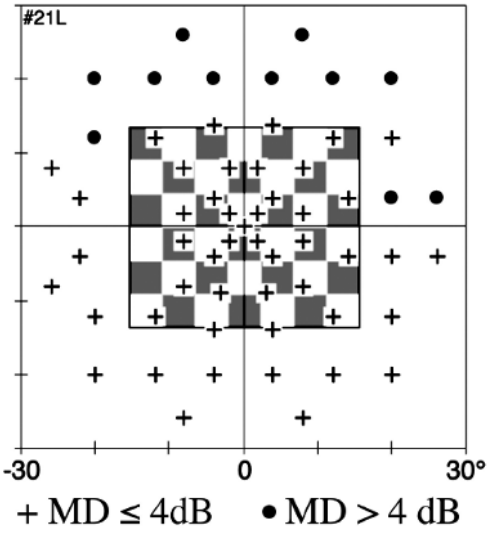

Fig. 5.8 A visual field from the left eye of a glaucoma patient. Black discs denote pathologic field locations with MD > 4 dB. The checkerboard pattern in the center represents the size of a typical PERG stimulus. Even though there is no field defect in the region covered by the PERG stimulus, the PERG response is often abnormal. This suggests that the PERG picks up non-focal damage in glaucoma. (From [5], with permission)

In a more recent prospective study [95], the Freiburg group 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), the sensitivity and specificity of the technique can be compared. The sensitivity/specificity analysis (also known as receiver operating characteristics analysis) are shown in Fig. 5.7. 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.

5.2.4.4 PERG May Reveal "Panretinal Ganglion Cell Damage" in Glaucoma

In hindsight it was unexpected for the PERG to detect glaucoma changes so effectively, considering that the stimulus covers only the central 15°, whereas 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 [13], but to test this more directly the Freiburg group 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. 5.8. In 13 of 18 such eyes (from 16 patients) with a normal field in the stimulated area, we obtained a pathological PERG [15]. 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°×15° patch are already small, and will be further reduced if even smaller patches are used for stimulation; therefore, mfPERG studies are hampered by small responses and there are only three reports so far on mfPERGs and glaucoma [56, 60, 89]. These studies report, as expected, that mfPERG amplitudes are reduced in glaucoma patients and furthermore indicate that the PERG reduction does not appear to be in a topographical relationship to the visual field loss observed in these patients. While these data support the above interpretation that the PERG is affected „panretinally" in glaucoma, they also indicate that glaucoma detection does not benefit from the spatial resolution provided by the multifocal approach at the expense of reduced signal-to-noise ratio; therefore, while the mfPERG might have the potential to enhance our knowledge of the pathophysiology of glaucoma, we would at this time not consider it useful to aid in the early detection of glaucoma.

Summary for the Clinician

- In order to reduce the interindividual amplitude variability, a PERG ratio can be calculated where the PERG amplitude to small checks is divided by the PERG amplitude to large checks in the same patient.
- In a prospective study the PERG ratio was shown to identify eyes at risk before manifest field damage.
- As the PERG ratio is affected by visual acuity, the "Freiburg PERG-paradigm" can only be applied on eyes with a visual acuity ≥ 0.8.

5.3 VEP Recordings in Glaucoma

5.3.1 Conventional VEP Recordings in Glaucoma

Any neural signal that reaches the visual cortex must have passed the layer of ganglion cells in the retina; thus, cortical VEP recordings offer another electrophysiological test of ganglion cell function. In glaucoma patients a delayed latency and/or a reduced amplitude of the major positive VEP component near 100 ms (P100) were reported by different studies [22, 69, 76]. Parisi [76] performed a simultaneous recording of PERG and VEP responses from normal subjects, patients with primary open-angle glaucoma (POAG), and patients with ocular hypertension (OHT). Besides PERG amplitude changes, VEP amplitudes were significantly reduced in POAG eyes, whereas in OHT they were similar to controls. Moreover, the retino-cortical signal transmission time, as assessed by the difference between VEP and PERG latency, was longer in POAG patients and inversely related to PERG amplitude; thus, retinal ganglion cell degeneration is accompanied by a slowed signal transmission in the visual pathway that can be assessed by VEP recordings.

None of the above-mentioned VEP studies tested the prognostic value of VEP amplitudes and latencies for an early detection of glaucoma. Recently, a „blue-on-yellow" VEP method had been presented as a functional test of the blue-sensitive S-cone pathway [59] that may be used for early detection of glaucoma. This S-cone pathway is affected in glaucoma before standard subjective perimetry as has been shown by psychophysical findings [49, 88]. Horn et al. [46] recorded blue-on-yellow VEPs in a group of patients with pre-perimetric glaucoma and showed that VEP progression of glaucomatous optic nerve damage was associated with a significant prolongation of the VEP latency 2 years before morphological changes were evident.

The VEP recordings depend on both retinal activity and the neural conduction along the post-retinal visual pathway; thus, VEP amplitude and latency measures may be confounded by factors independent of glaucomatous damage of retinal ganglion cells. Parisi [77] compared PERG and VEP data with nerve fiber layer (NFL)

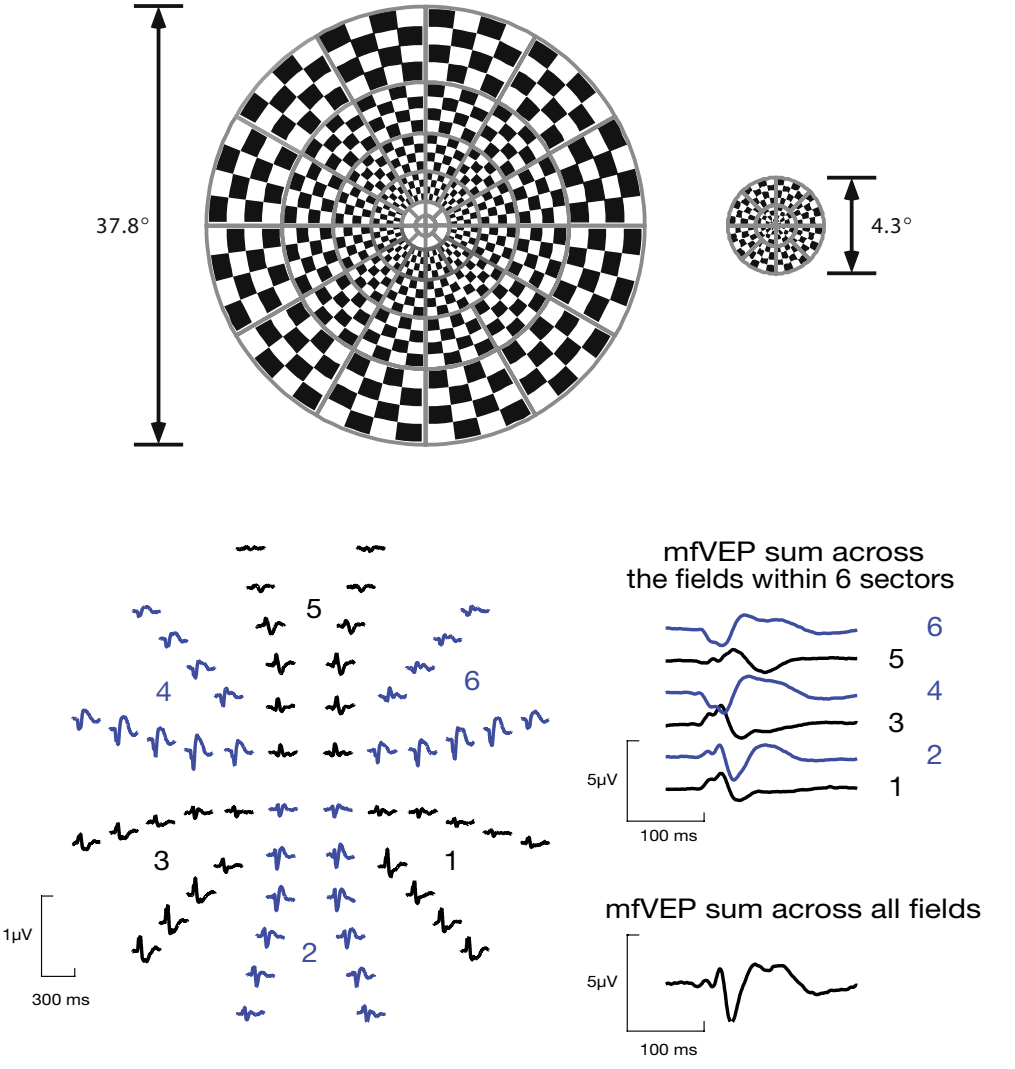

Fig. 5.9 Multifocal VEP (mfVEP) recordings. Top: "Dartboard" stimulus with 60 stimulus fields, each containing a checkerboard pattern that is reversed in contrast to evoke a local mfVEP for the corresponding part of the visual field. Bottom: Grand mean mfVEP traces across 30 visually normal subjects. The waveform of mfVEP traces varies very strongly which can be seen in the mfVEP sum across the stimulus fields in different sectors (1–6) of the visual field. The main reason for this variability is the individual folding of the cortical surface.

thickness data as assessed by optical coherence tomography in glaucoma patients. While amplitude and latency were abnormal for both PERG and VEP recordings, only PERG changes were correlated with NFL changes, whereas no correlations between NFL and VEP parameters were found.

Summary for the Clinician

- In glaucoma patients a delayed latency and/or a reduced amplitude of the major positive VEP component near 100 ms (P100) were reported by different studies.
- The "S-cone VEP" may help to improve the early diagnosis of glaucoma.

5.3.2 Multifocal VEP Recordings in Glaucoma

Baseler et al. [18] were the first to record a multifocal VEP (mfVEP). They scaled the size of local checkerboard patterns inversely to the cortical magnification factor for the corresponding eccentricity to activate a similar number of cortical neurons for all parts of the stimulated visual field. In contrast to multifocal ERG recordings the waveform of mfVEP traces varies very strongly even for normal subjects (Fig. 5.9). This variation can be found both when comparing different field locations in the same subject and when comparing the same field location between different subjects. The variation ranges from amplitude differences and inversions of polarity to nearly flat waveforms which might be misinterpreted as objective evidence for a scotoma [45, 55]. The main reason for this variability is the individual folding of the cortical surface as some cortical VEP generators may not project a signal onto a pair of recording electrodes, although visual function is normal in that part of the visual field. Consequently, a latency analysis is difficult in mfVEP recordings as a specific mfVEP peak (e.g., > 120 ms) may be interpreted as either a delayed component or a polarity-inversed component without increased latency.

During the past years many improvements have been introduced in the mfVEP recording and analysis procedures that helped to overcome the problem of interindividual variability and false scotomas. By performing multichannel recordings the chance to pick up a signal from at least one pair of electrodes can be increased significantly [44, 53]. An arrangement of several electrodes placed close (about 4 cm) to a common reference point near the inion has been shown to minimize the number of false scotomas. A reduction of mfVEP magnitude variability was achieved in different ways. Klistorner and Graham [54] found a correlation of mfVEP amplitudes and spontaneous EEG magnitudes and proposed the common shielding of intracortical mfVEP and EEG potentials as the source for this correlation. Klistorner and Graham [54] showed that the mfVEP can be normalized by the EEG magnitude which may reduce interindividual amplitude variability [54].

Hood et al. [43] presented a method to detect monocular scotomas by an interocular comparison of mfVEP responses within the same subject. As both eyes project to the same cortical surface, a flat mfVEP trace in one eye cannot be traced back to an unfavorable location of the generator when the stimulation of the other eye evokes a significant mfVEP for the same field. Of course, this methods fails if both eyes are involved in a pathological process. For the more general case of binocular involvement in glaucomatous defects Hood et al. [45] developed a method to detect mfVEP magnitude losses by analyzing the signal-to-noise ratio for each stimulus field which helps to avoid the misinterpretation of pure noise responses [105]. The calculation of the signal-to-noise ratios reduces interindividual variability in a similar way as the EEG-scaling method mentioned above [54]. The specificity of the scotoma detection will be enhanced if the criteria for scotoma detection are extended from the analysis of single stimulus fields to spatial patterns of neighboring visual field locations; however, such a pooling of mfVEP data across stimulus fields reduces the spatial resolution of the method [32, 41].

The above-mentioned improvements of the mfVEP recording and analysis strategies have helped to establish the mfVEP methods as a new

tool for the diagnosis of glaucoma. Hood et al. [42] demonstrated that Humphrey visual fields (HVF) and monocular mfVEPs show a comparable number of defects in patients with early to mild glaucomatous damage. With the addition of the interocular test, the mfVEP showed more abnormalities than HVF; however, although there were abnormalities detected by the mfVEP that were missed by the HVF, the reverse was true as well. Goldberg et al. [32] reported that mfVEP testing detected scotomas in nearly all cases of glaucoma where field defects had been established on subjective testing. They also found that about 60% of the subjects with glaucoma who had a fellow eye with a normal visual field demonstrated abnormal mfVEPs in that eye. As it is very likely that the fellow eye of a glaucomatous eye will develop glaucoma in the future, the mfVEP defects may indicate an increased sensitivity of the mfVEP method to detect early glaucomatous damage when compared with static perimetry; however, until the power of the mfVEP for an early detection of glaucoma has been validated by longitudinal studies, the major field of application for mfVEPs might be the follow-up of the course of the disease where mfVEPs may supplement static perimetry.

Summary for the Clinician

- In recent years the multifocal VEP (mfVEP) has been established as a new tool for the diagnosis of glaucoma.
- mfVEPs may supplement static perimetry in the follow-up of glaucoma in the future (Table 5.1).

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