ESSENTIALS IN OPHTHALMOLOGY

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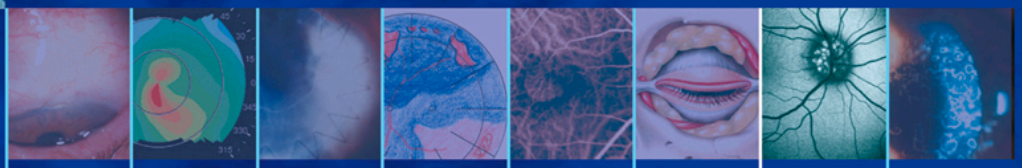

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Pediatric Ophthalmology, Neuro-Ophthalmology, Genetics

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Chapter 9

Investigating Visual Function with Multifocal Visual Evoked Potentials

9

Michael B. Hoffmann

Core Messages

- With multifocal visual evoked potentials (mfVEPs) the visual field can be sampled for response abnormalities. Thus, mfVEPs open the possibility of an objective visual field test. The issue, however, is greatly complicated by the variability of the responses across the visual field and between subjects.
- Cortical morphology dictates the mfVEP shape and influences mfVEP magnitude; consequently it is one important cause of the variability of mfVEPs. Thus for some visual field locations severe signal loss can occur, which mimics scotomata. The number of these spurious scotomata can be reduced by recording from multiple electrodes. To account for the cortical magnification of the visual field representation specifically scaled circular checkerboard patterns are used for stimulation.
- While different strategies proved successful for the evaluation of mfVEP magnitude and latency, root-mean-square calculations and correlations of the responses with reference traces have the advantage of being based on a number of points as opposed to single peak values and yield reliable estimates of response magnitude and latency.
- Estimates of mfVEP magnitude, latency, and cortical topography are valuable tools for the assessment of visual function. Multifocal VEP magnitude is particularly valuable for an objective visual field assessment in glaucoma patients. Multifocal VEP latency measures promise further insight into visual system abnormalities in patients with optic neuritis and multiple sclerosis. Multifocal VEP topography can help to detail malformation of the optic chiasm, e.g., in albinism.

9.1 Introduction

It did not take long after the pioneering work of Sutter [1, 2, 3] that the potential of the multifocal stimulation technique to describe the visual field topography of visual dysfunction was recognized. Clearly, both the electroretinogram (ERG) and the visual evoked cortical potential (VEP) can be combined with the multifocal stimulation technique [3, 4]. This opens the possibility of a spatially resolved identification of (1) dysfunction of the retinal photoreceptors and bipolar cells with multifocal ERG (mfERG) and (2) dysfunction of the visual pathway with the multifocal VEP (mfVEP). However, while mfERGs have quickly proved to be useful for the assessment of many aspects of visual dysfunction [5], mfVEPs have entered the field more slowly. This is primarily due to methodological problems that are intrinsic to mfVEPs. Multifocal potentials recorded from the

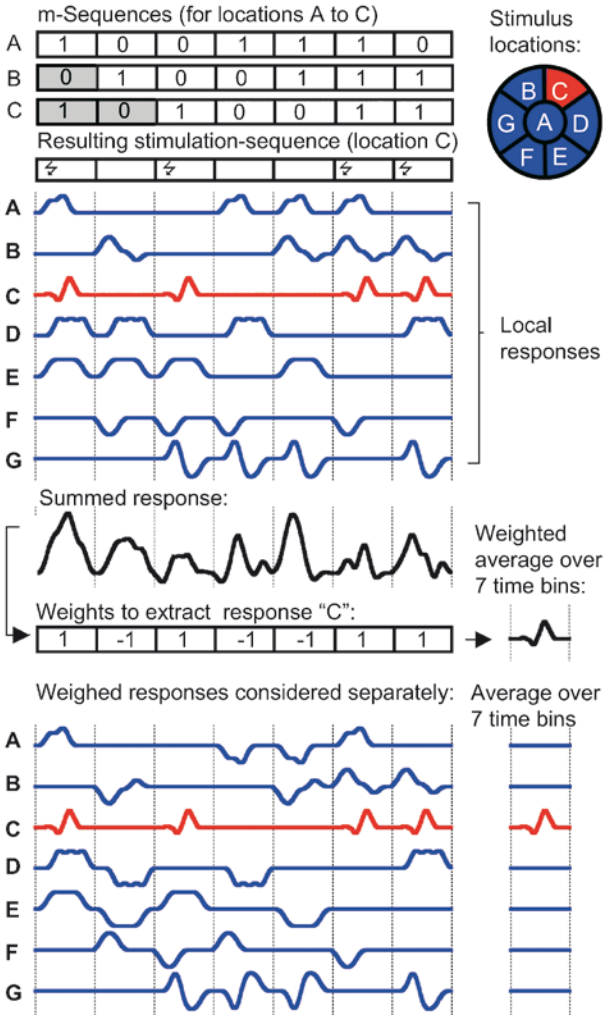
visual cortex display great variability across the visual field within and between subjects. These fluctuations of response sizes make it difficult to assess whether an unresponsive visual field location has a methodological cause or indicates a veridical scotoma. Indeed, Baseler et al. [4], in their pioneering study, attributed mfVEPs only little potential to contribute to clinical visual field testing. Since then, endeavours to utilize mfVEPs for a functional assessment of the activity in the visual cortex have not ceased and substantial improvements of the procedure in the late 1990s, namely multi-electrode recordings and refined analysis strategies, spurred off a steady stream of investigations. These studies finally succeeded in rendering approaches that enable us to conduct an objective visual field test based on mfVEPs [6]. As will be shown below, the assessment of the magnitude, latency, and topography of cortical responses in diseases such as glaucoma, optic neuritis, and albinism are striking examples of the potential of mfVEPs to enhance our understanding of pathologies of the visual system.

9.2 Multifocal Principle and Characteristics of Multifocal VEPs

9.2.1 Basics – Multifocal Stimulation, First- and Second-Order Kernels

The multifocal technique enables one to extract separate responses from a number of stimulated visual field locations, typically more than 50, within a short recording interval, typically 8 min for one monocular recording. Instead of measuring the response for each location separately, in the multifocal approach the entire array of locations is stimulated quasi-simultaneously, in a manner that allows for the extraction of the responses of each single location from the summed response (Fig. 9.1). The extraction of the responses is possible as the stimulation sequences are known and have been selected to fulfil a number of requirements, particularly mathematical independence. The sequences are termed binary m-sequences, i.e. they determine two stimulus states, e.g. stimulus pulse and no stimulus pulse. They also have the advantage that from one m-sequence other mathematically independent m-sequences can be derived by the selection of a different starting point within the m-sequence. This is illustrated in the schematic of Fig. 9.1a where m-sequences for locations B and C are shifted by one and two elements, respectively, compared to A. Thus, each visual field location will be stimulated with the same sequence, but with a different starting point. Knowledge of both the applied m-sequence and the different starting points enables one to extract the response for one particular visual field location with a cross-correlation [2]. The basic principle is illustrated in Fig. 9.1a for a or didactive purposes simplified (e.g., only seven stimulus locations, a very short m-sequence of only seven elements, responses in non-overlapping time bins) schematic. For simplicity the extraction of a response to a flash

► **Fig. 9.1a,b.** **a** Schematic illustrating the basic concept of the multifocal principle. A for didactic puposes substantially simplified example of simultaneous stimulation of only seven locations with a very short stimulation sequence of seven elements is used for this illustration (after Sutter [1], details given there). Each location is stimulated with the same binary m-sequence (1: stimulus pulse, 0: no stimulus pulse), but shifted in time (as indicated by the shaded bins for locations b and c, which comprise the end of the first m-sequence for location A). For each location a sequence of responses (*blue traces*) is elicited by its stimulation sequence; for illustrative purposes each location is given a different response shape. An electrode recording from all locations will yield the summed response (*black trace*). To extract the response for location c (indicated in *red*) each bin of the response sequence is assigned the weight –1 or 1, for 0 (no stimulus) or 1 (stimulus) in the m-sequence for c, respectively. The weighted average over the seven time bins yields the response of location C, as the responses from the other locations cancel out, while those from C are extracted (*bottom part* of **a**). **b** Derivation of the weights for location "c" from the stimulation sequences for the extraction of the first-order kernel (response to flash pulses; stimulation results in a positive, no stimulation in a negative weight) as used in **a**. The *bottom row* indicates the weights for the second-order kernel responses, i.e., the responses to stimulus changes, derived from the stimulation sequence (change of state results in a positive, no change in a negative weight) as for the extraction of pattern reversal mfVEP responses. It should be noted, however, that this is a schematic and substantially simplified example, and that in fact only longer sequences allow for the accurate extraction of the kernels (see text)



a

m-Sequence (for location C)

1	0	1	0	0	1	1

1st order kernel

Weights to extract response

1	-1	1	-1	-1	1	1
Stimulus:	↯		↯			↯	↯

2nd order kernel

Weights to extract responses:

	1	1	1	-1	1	-1
Stimulus:	■□	□■	■□	□■	■□	□■	■□

b

pulse, as used in standard mfERG recordings, is shown. In this case the first-order kernel is extracted, i.e. the response to one of two stimulus states, namely flash on. For the multifocal VEPs the matter is slightly more intricate, as VEPs are usually recorded in response to pattern reversal and not to flash stimuli. During pattern-reversal stimulation, a pattern is permanently present at each visual field location, and the two stimulus states are the two contrast polarities of this pattern. It is the change between the two states of the pattern that evokes the response. To extract the response to this change, the history of the sequence has to be taken into account, which requires the extraction of higher-order kernels. Specifically, to obtain the response to the pattern-reversal stimulation the so-called first slice of the second-order kernel is extracted (see schematic in Fig. 9.1b for the principle behind the derivation of the weights). It should be noted that much longer m-sequences than for those of the schematic in 9.1 are actually required. In fact it is evident from figure 9.1 that the short sequences used would not even allow for the distinction of first-order and second-order kernel responses: the weights for the second-order kernel for location C are the same as those for the first order kernel for location F. In a standard recording of around 8 min duration, the m-sequences consist of more than 32,000 elements, where the duration of an element equals one monitor frame interval, e.g. 13 ms. Finally, it should be noted that recently an alternative approach to obtaining multifocal responses, which is based on a multiple regression framework, has been put forward [7].

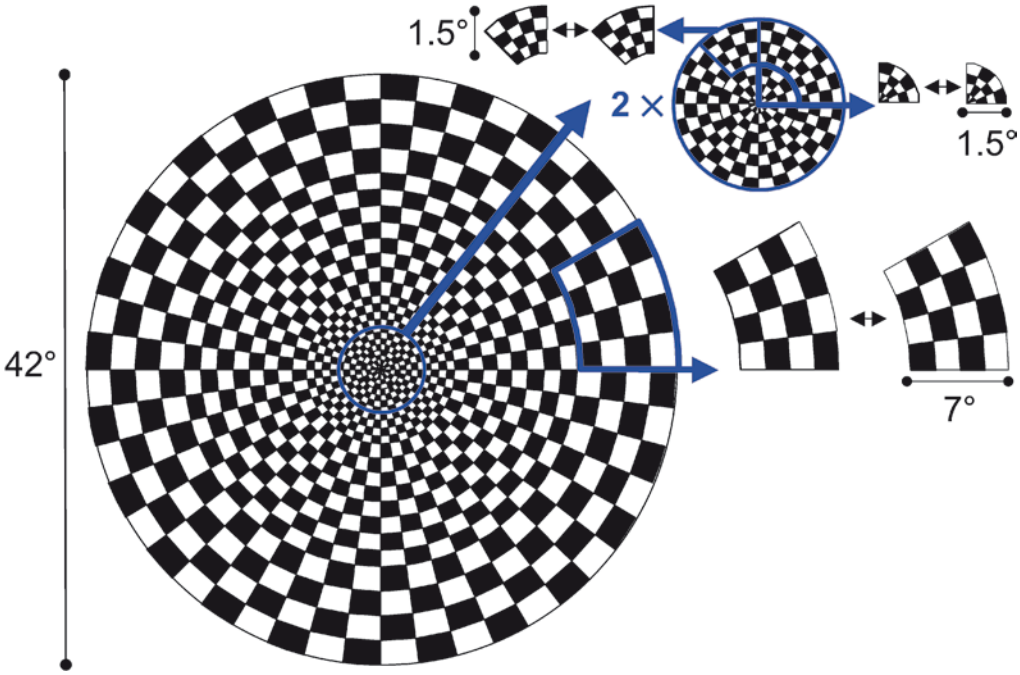


Fig. 9.2. Circular dartboard pattern used for mfVEP recordings. The stimulus comprises 60 4-by-4 checkerboard patches that increase in size with eccentricity. Three individual patches are isolated and the two states of the pattern-reversal stimulus are indicated. For clarity the centre is enlarged by a factor of two in the *inset*, as indicated by "2 x"

Summary for the Clinician

- With the multifocal technique separate responses from many visual field locations, e.g. more than 50, can be obtained within a short time interval, e.g. 8 min per recording.
- Responses to different stimuli, e.g. flash or pattern reversal, can be extracted from summed responses recorded with a single electrode pair.

9.2.2 Stimulus Display for mfVEP Recordings

Conventional checkerboard patterns are usually not applicable to mfVEP recordings [4, 8] and circular checkerboards are used instead (Fig. 9.2). The reason for this is the way in which the visual field is represented on the visual cortex. Due to the cortical magnification of the centre, the central visual field covers a greater area of visual cortex than the periphery. Consequently, to obtain sizeable mfVEPs from both the centre and the periphery the cortical magnification has to be taken into account, presenting small stimuli in the centre and greater stimuli in the periphery. The standard way to achieve this is to use a scaled circular checkerboard pattern, i.e. a dartboard-like pattern. An example of a typical mfVEP stimulus is depicted in Fig. 9.2. Here, a circular checkerboard subtending 42° of visual angle is subdivided into 60 single sectors. Each sector comprises a 4-by-4 checkerboard pattern, which proved to be an effective stimulus [9]. Responses from 60 visual field locations can be obtained with this stimulus, with the highest spatial resolution, around 1.5° sector width, in the centre and the lowest resolution, around 7° sector width, in the periphery. The responses are usually displayed as a re-projection of the signals to the visual field locations that evoked them (e.g. Fig. 9.3). It should be noted, however, that for ease of the illustration the responses from different eccentricities are usually depicted in an equidistant manner, while the actual stimulus layout is approximately m-scaled. This discrepancy between the mfVEP stimulus and the response display has to be taken into account when reading the mfVEP displays. Finally, a note on the stimulation mode should be added. While pattern-reversal stimulation is the most commonly used for mfVEP recordings, recent investigations indicate that another stimulation mode, i.e. pattern onset from an equiluminant grey background, is also an effective VEP stimulus, particularly in the central visual field [7, 8, 10, 11, 12, 13].

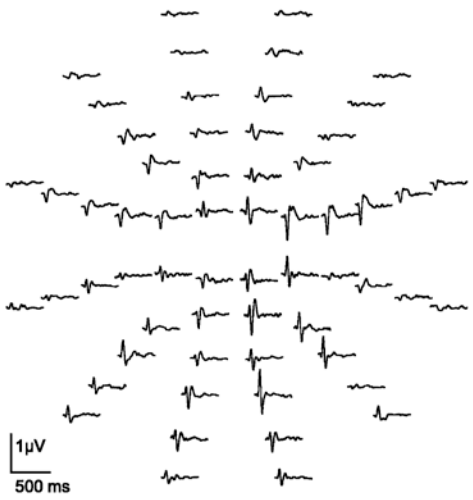
Summary for the Clinician

- Scaled circular checkerboard patterns are used in mfVEP recordings to compensate for the magnification of the cortical representation of the central visual field.
- For ease of the illustration, however, the responses from different eccentricities are usually depicted in an equidistant manner.

9.2.3 Recording mfVEPs and Practical Considerations

In general, the same amplifier settings and electrodes as for conventional VEP recordings [14] can be used for mfVEP recordings. However, different recording sites are recommended for the mfVEP. Optimal are occipital recording sites with an occipital reference [4, 15, 16, 17]. As will be detailed below, mfVEPs benefit from the use of additional lateral electrodes. Different arrangements were successful and an example of a multi-channel montage of three physical recording channels [18] is given in Fig. 9.4.

As for the conventional VEP, the quality of the retinal image is of major relevance for mfVEP recordings. Optical deficiencies such as refractive error or light scatter reduce responses particularly to the small central checks of the circular checkerboard pattern [19, 20]. Refractive error needs to be corrected carefully and other factors reducing the retinal image quality have to be taken into account for the assessment of the recordings.



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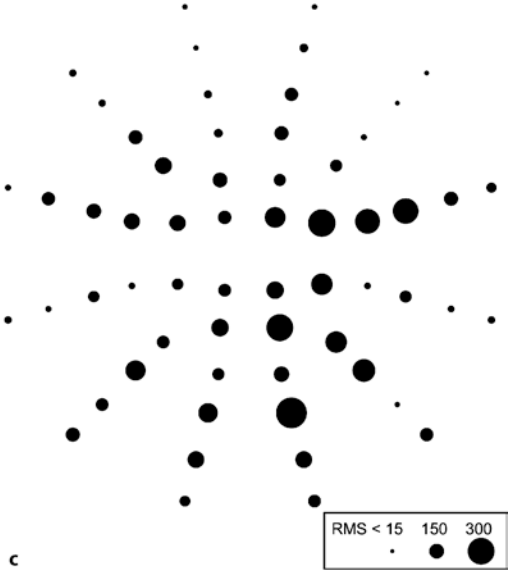

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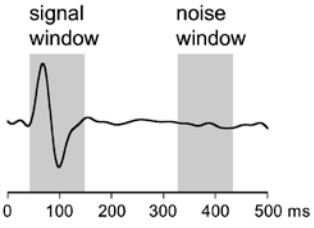


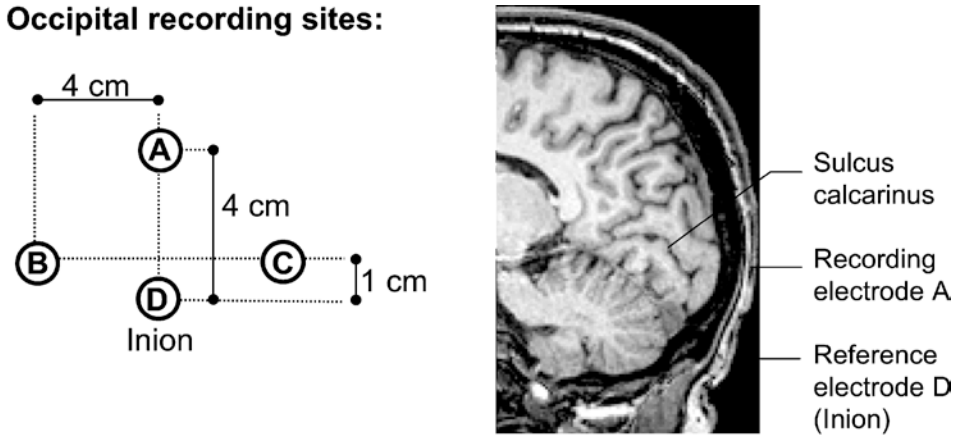
b

$$RMS_{signal} = \left[\sum_{t=45}^{150}(R_t - \mu_{45\ to\ 150ms})^2/m\right]^{0.5}$$

$$RMS_{noise} = \left[\sum_{t=325}^{430}(R_t - \mu_{325\ to\ 430ms})^2/m\right]^{0.5}$$

$$mnSNR_i = \frac{RMS_{signal\ i}}{\sum_{i=1}^{60} RMS_{noise\ i}/n} - 1$$

Fig. 9.3a–c. **a** Example of a pattern-reversal mfVEP recording from 4 cm above the inion referenced to the inion. mfVEPs are depicted as a re-projection to the visual field locations that evoked them. It should be noted that the responses from different eccentricities are arranged in an equidistant manner, while the actual stimulus layout is approximately m-scaled. Response strength and shape vary across the visual field. A typical feature of mfVEP traces, the tendency of a polarity reversal of the traces from the upper compared to the lower horizontal meridian, is evident. **b** Quantification of a response at a particular visual field location [29]: calculation of the root-mean-square, RMS, in the signal (45–150 ms) and the noise time window (325–430 ms) and of the signal-to-noise-ratio, SNR, from the signal RMS and the mean noise RMS over all 60 stimulus locations (µ=mean; *t*=time; *i*=stimulus location; *m*=number of samples; n=number of stimulus locations, here *n*=60). **c** RMS values derived from the traces in a, *symbol size* indicates the RMS value. The variability of the RMS values across the visual field corresponds to that of the response magnitude of the original traces shown in **a**



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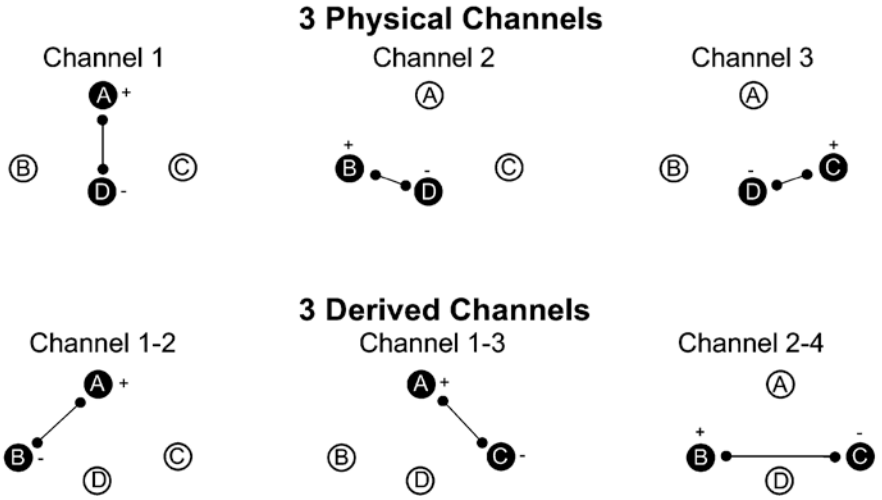


b

Fig. 9.4a,b. **a** Recording sites as proposed by Hood et al. [18]. **b** From three recording sites referenced to the inion (*D*) another three recording pairs can be derived. Thus electrical dipoles of different orientations can be tapped

During mfVEP-based objective visual field testing, subjects are not required to respond to the stimuli presented and concentration onto the stimulus does not appear to be of major relevance [21]. While this reduces the degree of cooperation that is required from the subjects, steady central fixation is still of essential importance. This is evident from studies with simulated fixation instabilities and with subjects that suffer from nystagmus [8, 20, 22]. During unsteady fixation particularly central responses are reduced; during steady misfixation the response maximum is likely to be shifted away from the stimulus centre.

While mfVEP responses do not appear to depend on age and race, there is a small influence of gender on the mfVEP: signal-to-noise ratios are about 10% greater in females than in males [23]. Finally, while recordings from children are always much more demanding than recordings from adults, Balachandran et al. reported mfVEPs from children as young as 5 years in a study investigating 70 children aged between 5 and 16 years [24]. This study suggests that the clinical assessment of visual function in children can be aided by mfVEPs.

Summary for the Clinician

- The quality of the retinal image is of major relevance for mfVEP recordings.
- Refractive errors need to be corrected for carefully for a recording.
- Other factors reducing the retinal image quality have to be considered for mfVEP assessment.

9.2.4 Dependence of mfVEPs on Visual Cortex Morphology

A typical example of mfVEP traces obtained from a single subject with a circular checkerboard pattern is depicted in Fig. 9.3a. Responses within 200 ms after stimulus onset are evident for many visual field locations and two main features of the mfVEP can be appreciated. Firstly, mfVEPs vary greatly in response magnitude across the visual field and there are occasional localized response reductions and even drop-outs at various locations. These occasional drop-outs are common in normal subjects and bear no relationship to veridical visual field defects, but unfortunately they mimic visual field defects. Secondly, it is evident from Fig. 9.3 that the trace shape varies across the visual field. In particular, there is a strong tendency for the response polarity to be inverted between upper and lower visual field responses. These two features underline that objective visual field testing based on mfVEPs is not trivial.

A major source of the inter- and intra-subject variability of the magnitude and shape of the responses is the cortical anatomy. Multifocal VEPs measured at a particular recording site strongly depend on the convolution of the visual cortex. An electrode pair is only able to pick up activity from a cortical generator if the generated electrical dipole projects onto this pair, which depends on the orientation of the dipole. The orientation of the dipole is assumed to be perpendicular to the cortical surface and is therefore closely linked to the cortical morphology, namely the convolution of a particular part of cortex. Thus mfVEP trace shape is tied to the cortical convolution. This has a number of important consequences. Firstly, as the retinotopic representation of the visual field in the visual cortex is laid out onto the convoluted surface of the occipital lobe, the orientation of the activated electrical dipole will depend on the visual field location stimulated. Consequently, some visual field locations will generate cortical activity that does not project onto a particular pair of recording electrodes and will therefore appear "silent". Secondly, the convolution of the cortex varies between subjects. Therefore, the position of the silent visual field locations is expected to vary between subjects. Thirdly, a particularly striking part of cortical convolution, namely that of the calcarine sulcus, explains the reversal of the response polarity of the upper compared to the lower visual field responses mentioned above. The pattern-reversal mfVEP is generated mainly in the primary visual

cortex [25], which is located in the calcarine sulcus of the occipital lobe. Here a retinotopic representation of the contralateral visual field resides, such that the upper part of the visual field is presented in the ventral bank of the calcarine sulcus and the lower part in the dorsal bank (Fig. 9.5). As a consequence of the representation of the upper and lower visual field on opposing banks of the sulcus, upper and lower visual field locations will activate dipoles of opposite polarity in the primary visual cortex. Thus mfVEP traces recorded with a vertical pair of occipital electrodes to stimulation in the upper visual field are polarity inverted compared to those to stimulation in the lower field (Fig. 9.5).

Due to the cortical convolution, some visual field locations generate cortical activity that fails to project signal onto a particular pair of recording electrodes. This activity, however, might project signal onto another electrode pair, which is sensitive to electrical dipoles of a different orientation. Thus additional recording electrodes increase the number of visual field locations from which a signal can be picked up [16, 18]. Therefore, in order to obtain responses from more visual field locations, mfVEPs are recorded from a number of electrodes. For each visual field location the recording pair with the greatest response is taken as an estimate of the response magnitude. Figure 9.4B illustrates an example of a montage resulting in six recording channels [18], namely three physical channels and three derived channels, which is successful in increasing the number of responsive visual field locations.

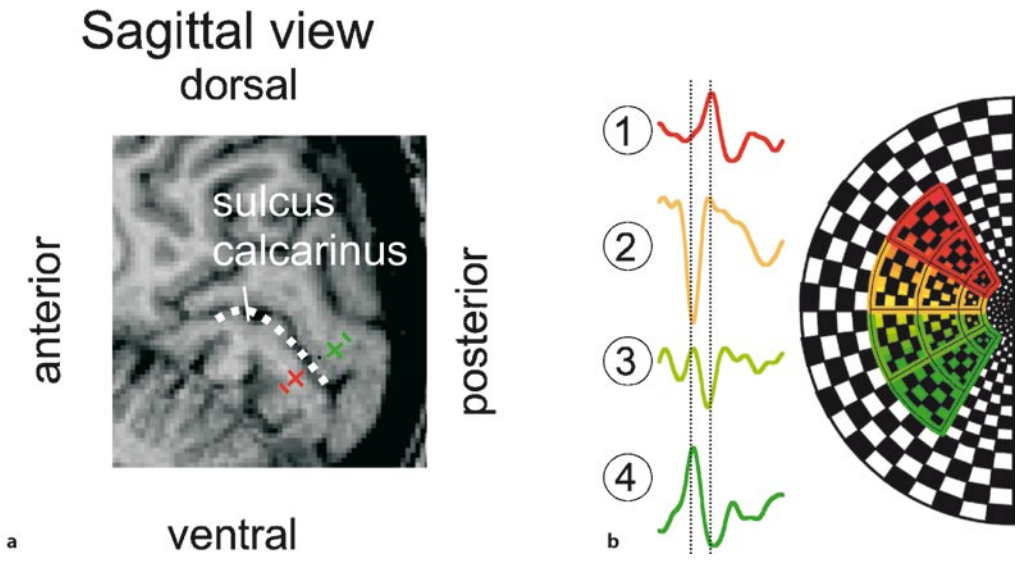


Fig. 9.5a,b. Relation of the polarity inversion of the mfVEPs to the anatomy of the calcarine sulcus (CS). **a** Schematic indicating that electrical dipoles, due to stimulation in the upper and lower field (in *red* and *green* respectively), have opposite polarity, as the upper and lower visual field are represented on the lower and upper bank of the CS. **b** mfVEPs recorded from 4 cm above the inion referenced to the inion, i.e. from a vertical pair of occipital electrodes (an epoch of 250 ms after stimulus onset is depicted). For the left hemifield, traces from three patches at the same polar angles are averaged together as indicated in the stimulus schematic on the *right*. Note that upper field responses are inverted compared to lower field responses (*dotted lines* at two particular response latencies are included as guides). The *colour code* indicates the presumed location of the generators of the traces 1 and 4 in the schematic **a** on opposing banks. As the lower horizontal meridian tends to be represented close to the fundus of the CS [55], it does not project much signal onto the derivation and results in smaller mfVEPS as is evident from trace 3 (see also Fig. 9.3)

Summary for the Clinician

- Cortical convolution dictates mfVEP shape, influences mfVEP magnitude, and is consequently associated with the occasional signal loss common to mfVEP recordings.
- The number of the resulting spurious scotomata can be reduced with multi-electrode recordings.

9.3 Assessment of mfVEPs

9.3.1 Response Magnitude

Multifocal VEP response magnitude is an important indicator of visual field defects. In some studies the peak-to-trough measure has been used systematically to quantify response magnitudes [16, 26], but there are problems with this mode of measurement. In particular, if responses are small and contaminated with noise, it can be difficult to detect the individual peaks and to decide whether a response was obtained for a particular visual field location or not. A more objective measure to quantify the response magnitude is the mean root-mean-square (RMS) calculated for a particular time window (Fig. 9.3b). The RMS measure has the great advantage that it does not depend on the identification of particular aspects of the response waveform and polarity – only the time window in which a response is expected has to be specified. As an example of this magnitude estimation, RMS values derived from the mfVEPs depicted in Fig. 9.3a are shown in Fig. 9.3c.

Response magnitudes can differ greatly between subjects. One way to deal with this problem is the interocular comparison of the responses, as similar response magnitudes are expected for both eyes of the same subject. Further, both eyes project to nearly identical parts of the retinotopic map in the visual cortex. As a consequence, signal drop-out due to cortical convolution should be similar for both eyes. Differences in the visual field maps of the two eyes must therefor be due to true scotomata and thus an objective visual field testing based on the interocular comparison of mfVEP responses can be established. The approach is successful [26, 27] (Fig. 9.6), but unfortunately it is limited to the detection of only a subset of visual field defects, namely those which are not homonymous. To detect homonymous defects a monocular test is necessary and consequently the problem of the interindividual variability of response magnitudes has to be overcome. This can be achieved by normalizing the responses upon an internal reference, e.g. the overall EEG level [28] or the noise level [29]. The latter approach shall be detailed here. Zhang et al. [29] determined two RMS amplitudes, one in a time window in which the signal is expected and one in a time window in which no signal but noise is expected (Fig. 9.3b). The ratio of these two RMS amplitudes can be taken as an estimate of the signal-to-noise ratio, SNR (Fig. 9.3b). Using SNR as a measurement of the response magnitude reduces the interindividual variability. Thus the SNR values obtained from a patient compared to those of a control population can be used to calculate the probability of a true visual field defect. It should be noted, however, that the statistics of the monocular analysis are not sim-

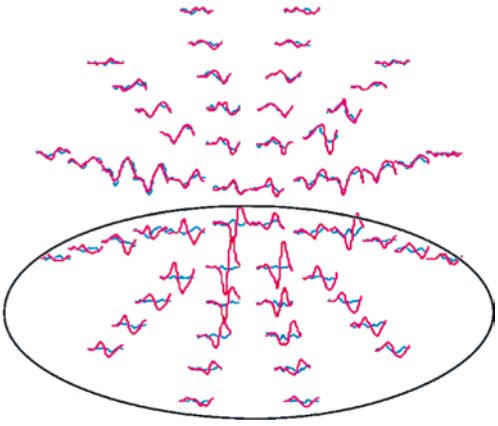


Fig. 9.6. Interocular comparison of mfVEP responses in a subject with glaucoma-related visual field defects for the right eye (*blue traces*; normal left eye: *red traces*). The responses within the ellipse are significantly smaller in the right eye. From Greenstein et al. [43], wich has further details (with permission copyright© 2004, American Medical Association. All rights reserved)

ple and caution has to be exerted in the interpretation of the results. For example in subjects with noisy records more spurious scotomata than expected by chance will occur. One way to increase the specificity of the detection of visual field defects, but at the expense of spatial resolution, is to define a true scotoma as the contiguous expanse of a number of silent visual field locations, e.g. a cluster of two to three silent locations [6, 30]. An example of an estimation of visual field defects from the interocular and monocular analysis is given in Sect. 9.4.1 (Fig. 9.7).

9.3.2 Response Latency

Similarly to the estimation of signal magnitude, mfVEP latency can be estimated based on a single peak analysis [9, 31]. As for the magnitude estimation, however, a single peak analysis requires the identification of individual components of the responses, which can be difficult for mfVEPs. Another way to determine whether a response is shifted in time relative to a reference trace is a cross-correlation of the two traces. This approach has two advantages to a single peak analysis: it is based on many data points and it takes the shape of the traces into account. A correlation of two traces yields a correlation coefficient, which can be taken as a measure of the similarity of the two traces. In a cross-correlation, one of the traces will be shifted with respect to the other and the correlation coefficient will be computed for each shift. The amount of shift necessary to obtain the highest correlation coefficient is taken as the latency difference. For the success of the technique it is important to select the appropriate reference trace. Several studies used the response of the fellow eye as a reference trace and thus determined interocular latency differences [18, 32, 33, 34]. Indeed, this way it is possible to pick up and quantify a physiological interocular latency difference, namely the delay of responses of the temporal relative to the nasal retina. Ganglion cell responses in the temporal retina are delayed compared to those of the nasal retina, as the action potentials of the ganglion cells in the temporal retina must travel further along unmyelinated axons to the optic disc than those from the corresponding nasal retina. Using mfERG components reflecting ganglion cell activity this delay was estimated to be up to 10 ms at around ±10° eccentricity [35]. The cross-correlation technique applied to mfVEPs yielded interocular latency differences of a similar magnitude, namely up to 11 ms [32] and 8 ms [34] (Fig. 9.8). This demonstrates the potential of the technique to quantify latency differences. As for the interocular magnitude comparisons, determining interocular response delays does not allow for the detection of abnormal latencies in patients in whom both eyes are affected. In this case a monocular test is required and the reference trace for each visual field location must be derived from a control population [33, 36]. As for the interocular comparisons, this procedure can be tested by the assessment of physiological latency effects, e.g. the well-known increase of VEP latency with age. This tendency is also evident from the monocular assessment of mfVEP traces. While the accuracy of these approaches to determine latency effects critically depends on the SNR of the signals [32, 36], they promise great potential for the assessment of disease-related latency changes.

Summary for the Clinician

- Due to small amplitudes and the variability of trace shape, single peak measures are problematic for the evaluation of mfVEP magnitude and latency.
- Instead, root-mean-square measures can be used to quantify mfVEP magnitude and to determine the signal-to-noise ratio of the responses.
- Latency deviations can be determined by cross-correlating the mfVEP trace with a reference trace.
- Interocular comparisons help to address the problem of interindividual mfVEP variability, but also strategies for the monocular assessment of mfVEP magnitude and latency have been developed.

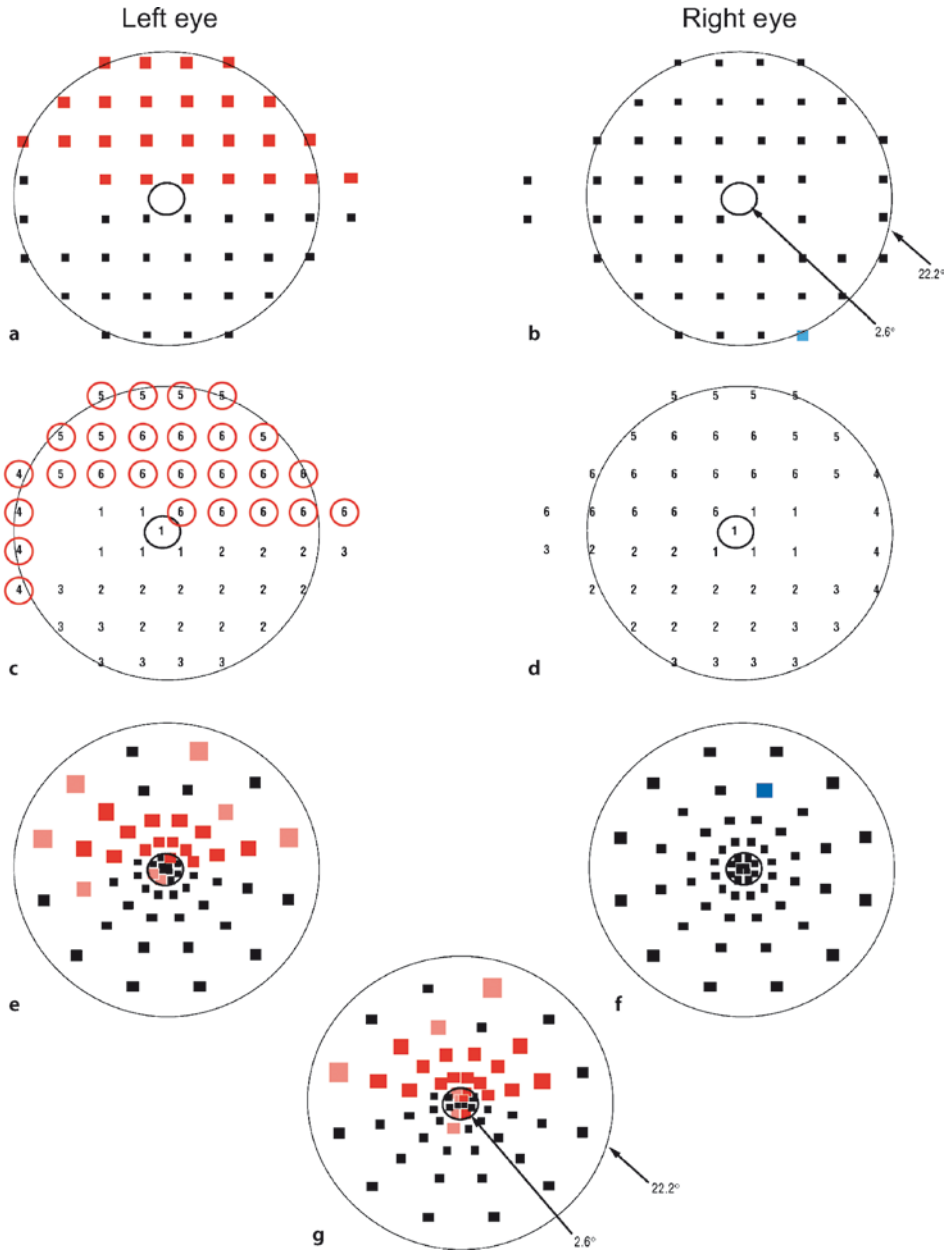
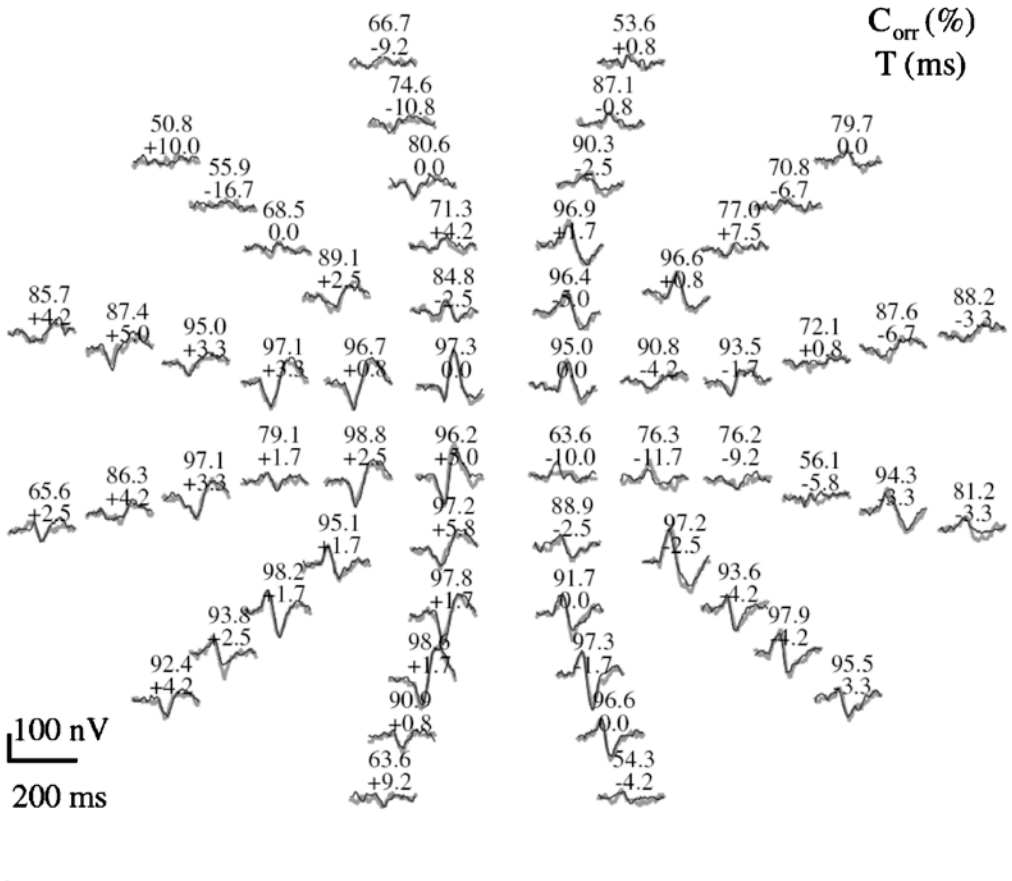


Fig. 9.7a–g. Comparison of visual field sensitivities derived from subjective visual fields (**a**, **b**; Humphrey: dark *red* and *light blue squares* indicate sensitivities that differ from normal at a significance level of 1% and 5%, respectively), confocal scanning laser ophthalmoscope (**c**, **d**; *red circles* indicate visual field locations corresponding to optic nerve head rim sectors that are abnormal in HRT II examination) and mfVEPs (**e**, **f** interocular comparisons; **g** monocular comparison; *dark* and *light coloured squares* indicate a reduction by 2.58 and 1.96 SD below mean values for the left and right eye in red and blue, respectively) in a subject with glaucoma and visual field defects for the left eye. All three techniques indicate similar visual field defects in this patient. From Greenstein et al. [43] (which has further details) with permission (copyright© 2004, American Medical Association. All rights reserved)



a

Fig. 9.8a. Example of the physiological interocular latency differences in normal controls. a Original mfVEP traces for the right and left eye in black and grey, respectively. Responses were recorded from an electrode 4 cm above the inion referenced to the inion. The interocular delay, T (ms) (negative and positive values indicate leading of the right or left eye, respectively), and the correspondence of the traces, C_{orr} (%), is given next to each response. Reprinted from Shimada et al. [34] with permission from Elsevier copyright©(2005)

9.4 mfVEP Investigations of Diseases

As multifocal techniques allow for the detection of localized damage, they provide a tool for objective visual field testing and thus promise great potential to aid diagnostics in clinical electrophysiology. Multifocal VEPs tap the visual cortex and can therefore be used to assess damage to its input stages, i.e. the outer and inner retina [6, 37], and the visual pathways [38, 39]. As the outer retina is the domain of the standard mfERG [5, 40], most mfVEP studies address changes to the cortical activity due to damage to the inner retina and upstream. MultifocalVEP studies with a clinical background have been conducted for a few years now. Although still at an initial stage, these studies indicate the potential of mfVEPs to contribute to this field. In this review an overview over three lines of research will be presented. These investigations in: (1) glaucoma, (2) optic neuritis and (3) albinism illustrate how mfVEP magnitude, latency and topography can contribute to our understanding of pathologies of the human visual system.

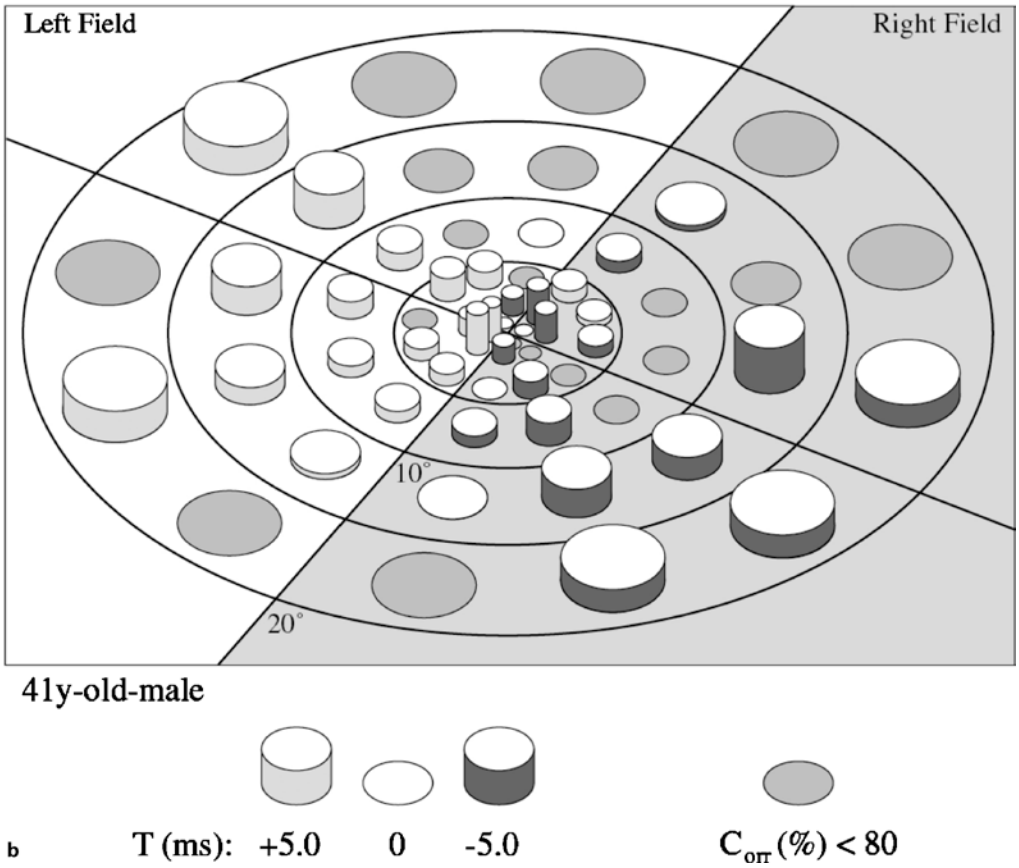


Fig. 9.8b. Illustration of the delay of the responses from the temporal retina relative to those from the nasal retina. Reprinted from Shimada et al. [34] with permission from Elsevier copyright©(2005)

9.4.1 mfVEP in Glaucoma

The majority of clinical mfVEP investigations were performed in patients suffering from glaucoma. In glaucoma, damage to the retinal ganglion cells causes visual field defects. At present, patients with suspected glaucoma, based on structural optic disc changes or high intraocular pressure, are assessed with static visual field perimetry, which requires the patients to judge the test stimuli subjectively. The possibility of an objective detection of glaucoma-induced visual field defects is opened by mfVEPs. Indeed, for glaucoma patients a great correspondence was demonstrated between subjective visual field perimetry and the assessment of visual field topography based on mfVEP magnitude [16, 26, 30, 41, 42]. They showed that the reduction of mfVEPs is a reliable indicator of visual field loss. Recently, Greenstein et al. [43] took this approach a step further and assessed in 40 eyes of patients with open-angle glaucoma whether visual field defects determined with automated static perimetry and with mfVEPs correlated with the visual fields defects predicted from anatomical measures of the optic nerve head. Healthy and glaucomatous optic discs were discriminated with confocal scanning laser ophthalmoscopy (Heidelberg retina tomograph II, HRT II) for six different sectors of the optic nerve head. Each of

these sectors was related to corresponding visual field regions. Thus, for six regions, visual fields were predicted from the state of the respective optic nerve head sectors. In 87% of the regions subjective automated static perimetry and objective mfVEP-based visual fields were in agreement. Of these regions, 85% were in agreement with the visual field defects determined from the anatomical measurements acquired with confocal scanning laser ophthalmoscopy of the optic nerve head. Although the three methods do not provide a perfect match, a great degree of correspondence between subjective and objective visual field measurements and anatomical measurements is present, which highlights the potential of mfVEPs to assist visual field perimetry in glaucoma patients (Fig. 9.7). In contrast to mfVEP magnitude, mfVEP latency appears to be only marginally affected by glaucoma. Rodarte et al. [44] demonstrated small mfVEP delays, i.e. of a few milliseconds rarely exceeding 10 ms, which affected only about 40% of the glaucoma patients tested. Interestingly, this contrasts with great latency effects of glaucoma reported in a recent conventional VEP study [45] and we are keen to learn in the future how this discrepancy resolves.

In glaucoma, do mfVEPs increase the yield of detecting early glaucoma? Reduced cortical responses might be evident before a visual field defect can be detected with subjective perimetry. As a consequence, mfVEPs might be a more sensitive indicator of localized ganglion cell damage. While there is at present no direct evidence indicating a sensitivity advantage of mfVEPs, there is some circumstantial evidence. Goldberg et al. [30] not only reported that glaucomatous eyes with abnormal subjective visual fields showed defects in the mfVEP assessment, but also that 60% of the fellow eyes with normal subjective visual fields showed defects. As the incidence of glaucoma in the fellow eye of a glaucomatous eye is very high, the authors of this study assumed that the fellow eyes with abnormal mfVEPs were already affected by glaucoma, but to an extent that did not yet influence subjective visual fields. While this interpretation of the results might suggest that mfVEPs might help to detect ganglion cell damage before subjective visual field perimetry, follow-up studies are needed to validate this presumption. Further it remains to be shown whether mfVEPs are more sensitive than pattern ERG at detecting early glaucoma [46, 47]. At present, evidence that mfVEPs might aid early detection is only indirect and we are eagerly awaiting studies that clarify this issue.

Summary for the Clinician

- Multifocal VEP magnitude allows for the objective detection of glaucoma-induced visual field defects.
- Thus mfVEPs can assist the follow-up of patients with glaucoma and might contribute to a better understanding of the underlying pathophysiological mechanisms.

9.4.2 mfVEP in Optic Neuritis

Optic neuritis (ON) is a syndrome characterized by an acute, unilateral loss of visual function. After an episode of ON, its diagnosis can be confirmed by the detection of a delay of the conventional VEPs [48]. Multifocal VEPs might aid the description and characterization of ON as it is expected to detect focal changes in the visual system that might not be evidenced by conventional-pattern VEPs, which reflect a summed response dominated by central vision. Furthermore, a more detailed description of the consequences of ON on the visual system with mfVEPs might help to differentiate between cases of ON that are associated with a risk of developing multiple sclerosis and those that are not.

There are at present only few studies investigating the association of ON with changes in the mfVEPs. An initial investigation of three patients with ON [49] suggested a correspondence of mfVEP response reductions and delays with defects in subjective visual field perimetry, albeit of variable degree. To minimize the blending of VEP responses from normal and abnormal visual field locations in ON, it appears therefore to be of benefit in ON patients to sample the visual field for VEP abnormalities in a spatially resolved manner with mfVEPs.

Based on MRI and clinical examinations Fraser et al. [31] subdivided a group of 64 patients with ON (past and acute) into 3 subgroups: no multiple sclerosis (MS), possible MS, and MS group. mfVEP response amplitudes deviated from those of normals in at least three adjacent visual field locations in 70%, 68% and 91% of the "no MS", "possible MS" and "MS" group, respectively, and response latencies deviated in 33%, 68%, and 100% respectively. An analysis of grouped responses from sectors with similar waveforms, taking responses of the entire visual field into account, indicated little latency deviations in the "no MS" group and substantial deviations in the "MS" group. Remarkably, the distribution of latency deviations in the "possible MS" group resembled a mixture of the other two groups. This suggests that mfVEP latencies might assist the identification of a patient's risk for future MS. In another study [33] it was investigated whether, in subjects with MS, mfVEP abnormalities are related to a preceding episode of ON. Multifocal VEP abnormalities were compared in subjects with MS that was associated with a history of ON and in those that were not. In both groups reduced amplitudes and delayed responses were reported. Hence, as the mfVEPs abnormalities are not exclusive to MS patients with a history of severe ON, they might also be indicative of other consequences of MS on the neural substrate. In summary, mfVEPs are able to detect VEP abnormalities associated with ON and MS and promise diagnostic value and insight into the underlying pathophysiological mechanisms. As the abnormalities can affect small portions of the visual field, mfVEPs might be more sensitive than conventional-pattern VEPs. Studies that directly compare the sensitivities of VEPs and mfVEPs in the detection of ON and MS are needed to clarify this issue.

Summary for the Clinician

- Multifocal VEPs are able to detect VEP abnormalities associated with ON and MS and promise diagnostic value and insight into the underlying pathophysiological mechanisms.

9.4.3 mfVEP in Albinism

The investigation of the visual pathways in albinism with mfVEPs is an example that demonstrates how the topographical information of the cortical responses can be used to describe abnormalities. Normally, the nasal retina projects to the contralateral hemisphere, while the temporal retina projects ipsilaterally. This normal projection of visual fibres from the retina is severely altered in albinism, where a great number of fibres from the temporal retina abnormally cross the midline and project contralaterally [50]. Conventional VEPs are an effective tool to demonstrate the misrouting of the optic nerves in albinism [51]. As each eye projects predominantly to its contralateral hemisphere in albinism, monocular stimulation of the central visual field elicits a greater activation in the hemisphere contralateral to the stimulated eye than in the ipsilateral hemisphere. This is evident from the VEP difference between electrodes over opposite hemispheres. Importantly, the polarity of this difference potential depends on the eye stimulated. A polarity inversion after stimulation of the right compared to the left eye indicates with great specificity and sensitivity misrouting of the optic nerves [51] (Fig. 9.9). By stimulating only parts of the visual field this VEP approach can be used to describe the extent of the projection abnormality [52]. Moreover, in combination with mfVEPs this approach opens the possibility of determining the visual field topography of the projection abnormality [22]. The use of multifocal VEPs to describe the visual field topography of the abnormality, however, is restricted to subjects without nystagmus as nystagmus greatly reduces mfVEP responses. An example of the visual field topography in a subject with albinism is given in Fig. 9.10. Here the polarity reversal was quantified by correlating with each other the traces obtained after left and right eye stimulation (Fig. 9.10b). Positive correlations indicate same polarity and normal projection; negative correlations indicate inverted polarity and misrouting. It is evident that the projection abnormality primarily affects a vertical stripe in the visual field centre, while the more peripheral part of the temporal hemiretina appears to revert to a normal projection pattern. This is in agreement with results obtained with conventional VEPs [52, 53] and functional magnetic reso-

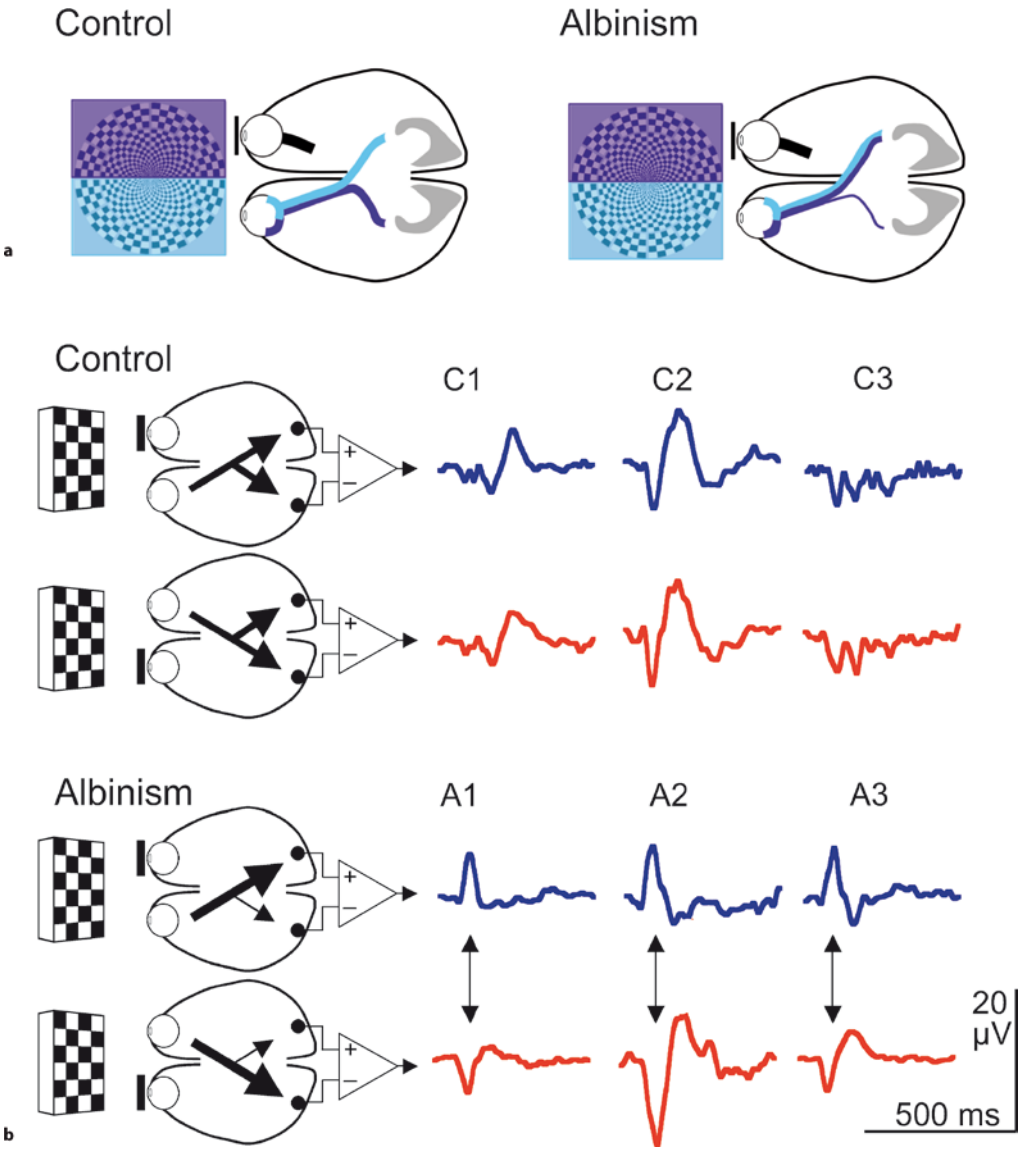


Fig. 9.9a,b. Schematic of misrouting of the optic nerves in albinism (**a**) and its detection with VEPs for three controls and three subjects with albinism (**b**). **a** Projection of the optic nerves of the left eye. Normally, the nasal retina projects to the contralateral and the temporal retina to the ipsilateral hemisphere. In albinism, part of the temporal retina projects erroneously to the contralateral hemisphere. The colour coding indicates on which hemisphere the hemifields are represented. **b** Detection of misrouting with VEPs. The inter-hemispheric VEP difference is recorded for left and for right eye stimulation. In the controls (*C1–C3*) no polarity reversal is evident between left and right eye responses. In the subjects with albinism (*A1–A3*) a polarity reversal between left and right eye responses is evident (*see arrows*), which is indicative of the misrouting of the optic nerves

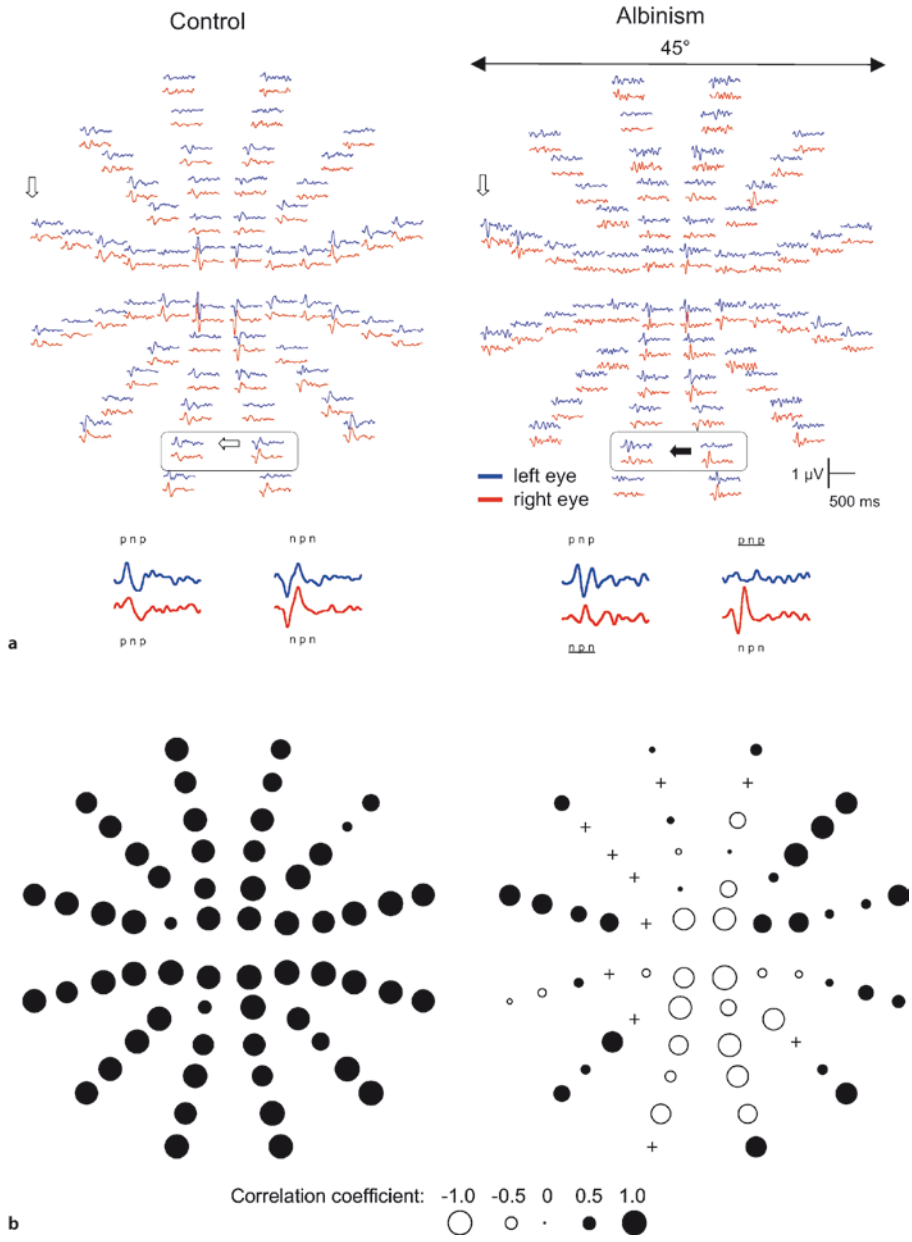


Fig. 9.10a,b. mfVEPs recorded from electrodes over opposing hemispheres (see Fig. 9.9) for a control subject (*left*) and a subject with albinism (*right*). **a** Raw traces from the left (blue) and right (red) eye as a re-projection of the visual field locations that evoked them. Note that the different eccentricities are depicted as equidistant while the actual stimulus layout is approximately m-scaled (applies also to **b**). Framed traces are enlarged for an easier assessment of the absence and presence of a polarity reversal in the control and the subject with albinism, respectively (note the succession of the peaks: *p*= positivity; *n*=negativity). **b** Quantification of the polarity inversion of the traces from both eyes as determined by correlating the traces with each other: parallel traces, i.e. no polarity inversion, yield positive correlation coefficients (*black symbols*), while anti-parallel traces, i.e. polarity inversion, yield negative correlation coefficients (*open symbols*). The latter indicate misrouting, which is evident along a central vertical part of the visual field of the subject with albinism (*right panel*). Crosses indicate sub-threshold responses, which cannot be assessed

nance imaging [54]. This study highlights how mfVEPs can contribute to a detailed analysis of visual pathway abnormalities. As mfVEPs allow for a detailed description of abnormal cortical representations of the visual field, they open the possibility of detecting small visual pathway abnormalities, which might not be uncovered by conventional VEP approaches.

Summary for the Clinician

- In patients without nystagmus mfVEP topography allows for the detection of misrouting of the optic nerves and thus opens the possibility of detecting even small visual pathway abnormalities.

9.5 Conclusion

The above examples demonstrate how mfVEPs can be used to describe the visual field topography of magnitude, latency and the topography of cortical responses, and how they can contribute to our understanding of diseases that affect the human visual system. Despite this great potential of mfVEPs to aid clinical diagnostic and basic research, they are used routinely in only a few centres. One reason is that the extraction of visual field maps from the mfVEP traces is demanding and that the required software is not readily available. Once this gap is filled the promising and rapidly developing mfVEP technique can be expected to assist clinical routine in the near future.

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