Multifocal ERG and VEP responses and visual fields: Comparing disease-related changes

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Multifocal ERG and VEP responses and visual fields: comparing disease-related changes

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Abstract. Static visual perimetry and the multifocal technique both measure the local effects of diseases of the retina and optic tract. The purpose here is to relate the measures obtained from each technique and to describe this relationship in some diseases. It is important to measure both the implicit time and amplitude of the multifocal ERG (mERG) or multifocal VEP (mVEP) responses. Some diseases affect one measure of the responses but not the other. The comparison of either measure to local sensitivity changes measured with static perimetry (e.g. the Humphrey 24-2 and 30-2) presents a problem. Different stimulus displays are employed. Further, the multifocal responses are displayed with arbitrary spacing between the responses. One approach is to measure the amplitude and implicit time of the multifocal responses and display these values on the same coordinates as in the visual field plots. This allows a qualitative comparison of fields and multifocal responses on the same scale. A second approach involves modifying the Humphrey perimeter software so that the test spots are placed in the centers of the multifocal stimuli (e.g. the center of each hexagon of the mERG display). A third approach involves estimating the thresholds for the regions of the multifocal display by interpolating from values at the standard Humphrey locations. The second and third approaches produce a one-to-one mapping of the multifocal and field measures and allow a quantitative comparison between the two. The relationship between visual fields and multifocal responses, determined through one or more of these approaches, is different depending upon whether the disease primarily affects the outer retina (retinitis pigmentosa), ganglion cell (glaucoma), or optic nerve (ischemic optic neuropathy and optic neuritis).

Key words: electroretinogram (ERG), glaucoma, multifocal, optic neuritis, retinitis pigmentosa (RP), visual evoked, visual evoked potential (VEP)

Introduction

Until recently, the behavioral visual field was the only practical way to measure the topographical effects of diseases of the retina and optic tract. With the development of the multifocal technology by Sutter and colleagues [1–3], a physiological measure of disease topography became possible. The purpose here is to examine the relationship between traditional static perimetry and the newer multifocal techniques, the multifocal electroretinogram (mERG) and the multifocal visual evoked potential (mVEP). In particular, we propose different approaches to comparing disease-related changes in the mERG or mVEP with changes in the visual field. The visual field discussed here is

the static field obtained with the Humphrey Field Analyzer, but the analyses described are easily transferred to other static fields obtained from other perimeters and can be generalized to kinetic perimetry as well. In addition, the particular relationship between multifocal measures and field changes will be considered for diseases that affect the outer retina (retinitis pigmentosa), ganglion cell (glaucoma), or optic nerve (ischemic optic neuropathy and optic neuritis).

Reasons for caution

Visual fields are threshold measures, while the mERG and mVEP are suprathreshold responses summed over numerous cells of different types. Thus, field changes measured physiologically need not agree with those obtained with behavioral techniques. In fact, there are several reasons why these measures might not agree. First, behavioral thresholds are determined by the activity of a subset of cells (e.g. the most sensitive of a class of cells), while the mERG and mVEP sum the activity of all cells. Second, the activity of cells damaged by disease may not be detectable in the physiological measure. A simple example is glaucoma where the primary cells involved, the ganglion cells, do not make a major contribution to the human mERG. Finally, while visual fields give us one number per location, the multifocal responses may change in amplitude, implicit time, or waveform. For different diseases, a different one of these three measures will correlate best with visual field changes. For example, implicit time of the mERG is often the best indicator of visual field damage in diseases of the outer retina. Thus, when visual field and multifocal measures are compared, we do not necessarily expect them to agree. We do, however, expect the comparison to provide valuable information about the sites and mechanisms of damage.

The problem: different spatial displays

Figure 1 shows typical displays used for obtaining the mERG and mVEP. The spatial extent and number of elements differ somewhat across laboratories and clinics. We have used 103 hexagons within a 25° field for the mERG (Figure 1A) and 60 sectors within a 18.5° field for the mVEP (Figure 1B). The key point here is that nearly everyone testing humans employs a display scaled with eccentricity for both techniques. On the other hand, the test points in static visual fields are usually equally spaced. For example, the most commonly used Humphrey fields are the 24-2 and 30-2 fields, where the locations tested are separated by 6° over a field that extends to either 24° or 30°. Figure 2A shows the mERG array overlaid onto the 30-2 locations; Figure 2B shows the mVEP display overlaid onto the 24-2 locations. There is no one-

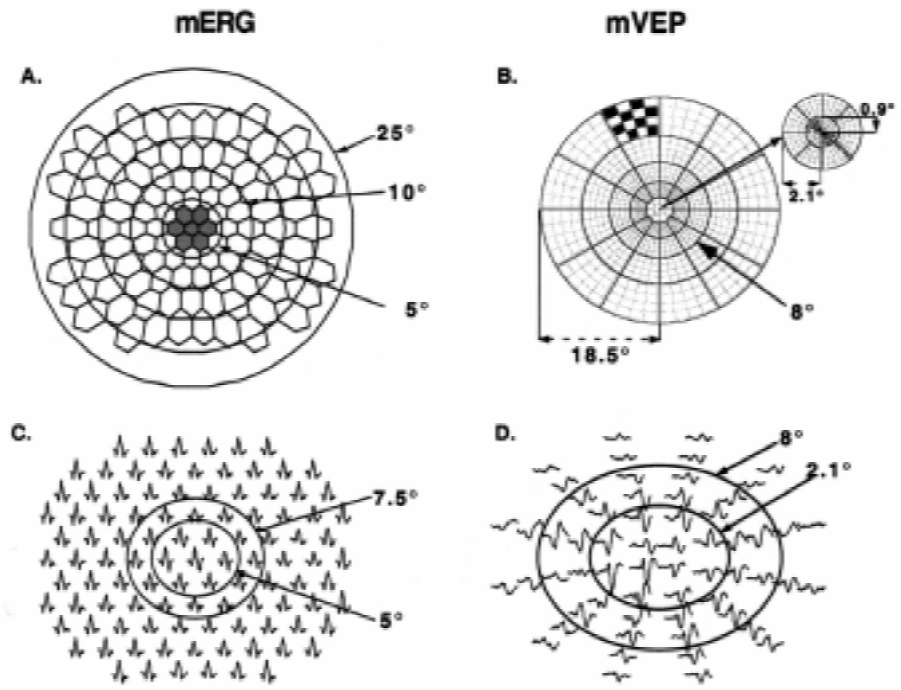

Figure 1. . Displays employed in mERG (A) and mVEP (B) recording with examples of mERG (C) and mVEP (D) responses.

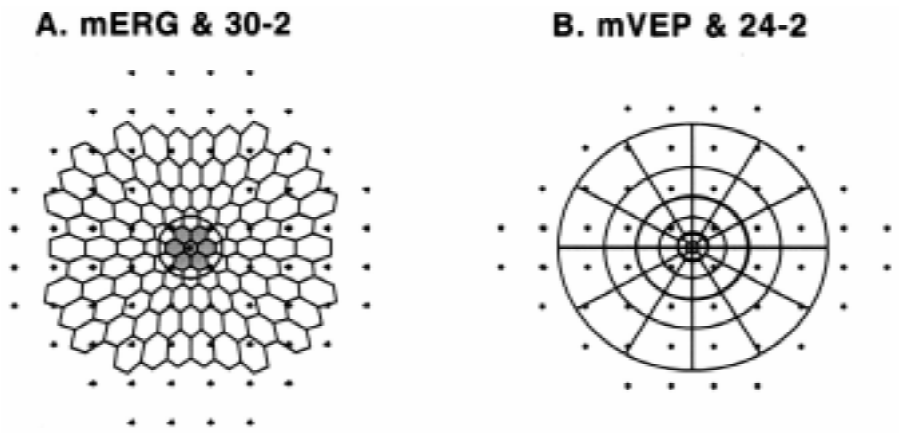

Figure 2. A. The locations of the test spots for the 30-2 (A) and 24-2 (B) Humphrey field in relation to the mERG (A) and mVEP (B) displays.

to-one correspondence between the Humphrey field and multifocal locations. To complicate matters further, the mERG and mVEP responses, typically, are not presented on linear coordinates. That is, the response waveforms must be arbitrarily positioned so that they do not overlap. This is most extreme in the case of the mVEP where 12 of the 60 mVEP responses fall within the central 2.1° (compare Figure 1B to 1D). Thus, comparison of multifocal responses to visual fields made by visual inspection can be very misleading. Below we consider three approaches to comparing multifocal responses and visual fields.

Methods

Details of some of the methods employed have been published previously [4–8]; the key aspects are summarized below.

Stimuli

The displays used for the mERG and mVEP recordings are shown in Figure 1A, B. For the mERG, the 103 element display (Figure 1A) was either a high contrast, black and white array with a mean luminance of 200 cd/m^2, or a 50% contrast, light and dark gray array with a mean luminance of 100 cd/m^2 [4, 5, 7]. For the mVEP display (Figure 1B), each of the 60 elements had a high contrast, 16-element reversing checkerboard, with a mean luminance of 100 cd/m^2 [8].

Electrophysiology

The mERGs were recorded with a Burian-Allen bipolar electrode. The mVEPs were recorded with gold cup electrodes placed at 4 cm above the inion (active), at the inion (reference), and on the forehead (ground). The continuous record was amplified with the low and high frequency cutoffs set at 10 and 300 Hz for the mERG and at 3 and 100 Hz for the mVEP (Grass PreAmplifier P511J, Quincy, Mass.). Pupils were fully dilated for the mERG; for the mVEP, the display was viewed with the natural pupil.

Visual field

In addition to Humphrey 24-2 or 30-2 fields, modified 103 Humphrey fields were obtained by modifying the Humphrey program so that the test spots (about 26’ in diameter, the same as for the 24-2 and 30-2 fields) were placed at locations in the field corresponding to the centers of the hexagons in Figure 1A [5].

Interpolated visual fields

Estimates of visual field thresholds at arbitrary locations can be made from the 30-2 or 24-2 fields. These interpolated visual fields were calculated in the following way. To estimate the sensitivity within a stimulus patch (i.e. a hexagon in the case of the mERG or a sector in the case of the mVEP), the antilog of the Humphrey deviation values was obtained for each test location, and these values were interpolated into a high resolution surface using a linear algorithm. The interpolated value for the stimulus patch was calculated as the average of all the interpolated values within the patch, and the log of this value was determined. For additional details on this technique, see [9].

Patients

All patients included here have been described in published reports. For ease of cross-referencing, the labels (e.g. P5) employed here to identify the patients are the same as in these reports. The figure captions contain the relevant patient information or citation. The patients P1 and P5 with RP are the same patients described in ref. [5]. However, the mERG and visual field results reported here are new and were collected 3.5 years after the tests reported in the earlier study.

Cranio-occipital variations and inter-subject variation in mVEP responses

The MRI scans from 50 normal individuals were examined in order to measure the location and angle of the calcarine sulcus relative to the placement of the electrodes for mVEP recordings. An experienced neuroradiologist marked the inion (technically the occipital protuberance) on a midsagittal view and located the calcarine sulcus on paramedian sagittal images. A line through the posterior portion of the calcarine intersects the skin at point c (see Figure 8). The location i′ of the inion at the skin (the position of one electrode) and 4 cm above i′ (the position of the other electrode) were marked. The distance d from c to i′ and the angle the calcarine makes with a line through i′+4 to i′ were determined (Figure 9A). The measurements made independently by two individuals were averaged after correcting for errors identified by large discrepancies.

Seven of the 50 individuals had mVEP recordings. For these seven, the amplitudes of the responses from the upper field were compared to those from the lower field using the following procedure. The root-mean-square (RMS) of each response was calculated over an epoch from 45 to 120 ms. The ratio of the RMS for corresponding upper and lower responses was determined for all 60 responses. The mean of these 60 ratios was taken as the subjects

ratio of upper to lower mVEP amplitudes. The log of this value is shown in Figure 9D.

This work was presented at the 2000 ISCEV meeting in Australia [10].

The mERG

Presenting mERG measures as 'fields'

Measures of the mERG. The mERG responses from two patients with retinitis pigmentosa can be seen in Figure 3. As we will see, it is important to measure both the amplitude and implicit time of the mERG responses [5]. Figure 3 shows the amplitude and implicit time changes for the responses associated with each hexagon. For the 'Amplitude Loss Field', the peak-to-trough amplitude of the mERG responses was expressed as a difference from control values in hundreds of nV. For example, –3 indicates that the peak amplitude of that response was 300 nV smaller than the mean value for the controls. For the 'Delay Field', the delay of the positive peak ('b-wave') of the response relative to control values is expressed in milliseconds. For example, 5 indicates that the implicit time of that response was 5 ms longer than the mean time for the controls. (See [6] for details on how amplitude and implicit time were measured.) In both amplitude and delay fields, light gray shading indicates values that are 2 to 4 s.d. from the mean normal value, and dark gray shading indicates values greater than 4 s.d.

A quantitative comparison of mERGs and perimetric fields

How do we compare the patients' visual fields to the patients' mERG responses? The fields are presented on linear coordinates, while the responses are spaced arbitrarily for clarity of presentation. However, the mERG amplitude and delay fields are in linear coordinates and can be compared directly to the visual fields. Figure 4A, B shows Total Deviation plots, which are part of the standard Humphrey report, for the 30-2 fields of patients P1 and P5 whose records are in Figure 3. Each number represents the difference, expressed in dB (1dB is 1/10 of a log unit), between the patient's threshold and a group of normals. Thus, -3 indicates that the patient's threshold is 3 dB (0.3 log unit) higher than that of a group of age-matched controls. Given the disease topography in patient P1, the comparison is relatively straightforward. In other cases, P5 for example, a visual determination of the relationship between mERG responses and the fields is difficult, because of the different spatial displays. There are two ways to solve this problem: the modified Humphrey field, and the interpolated field (see below).

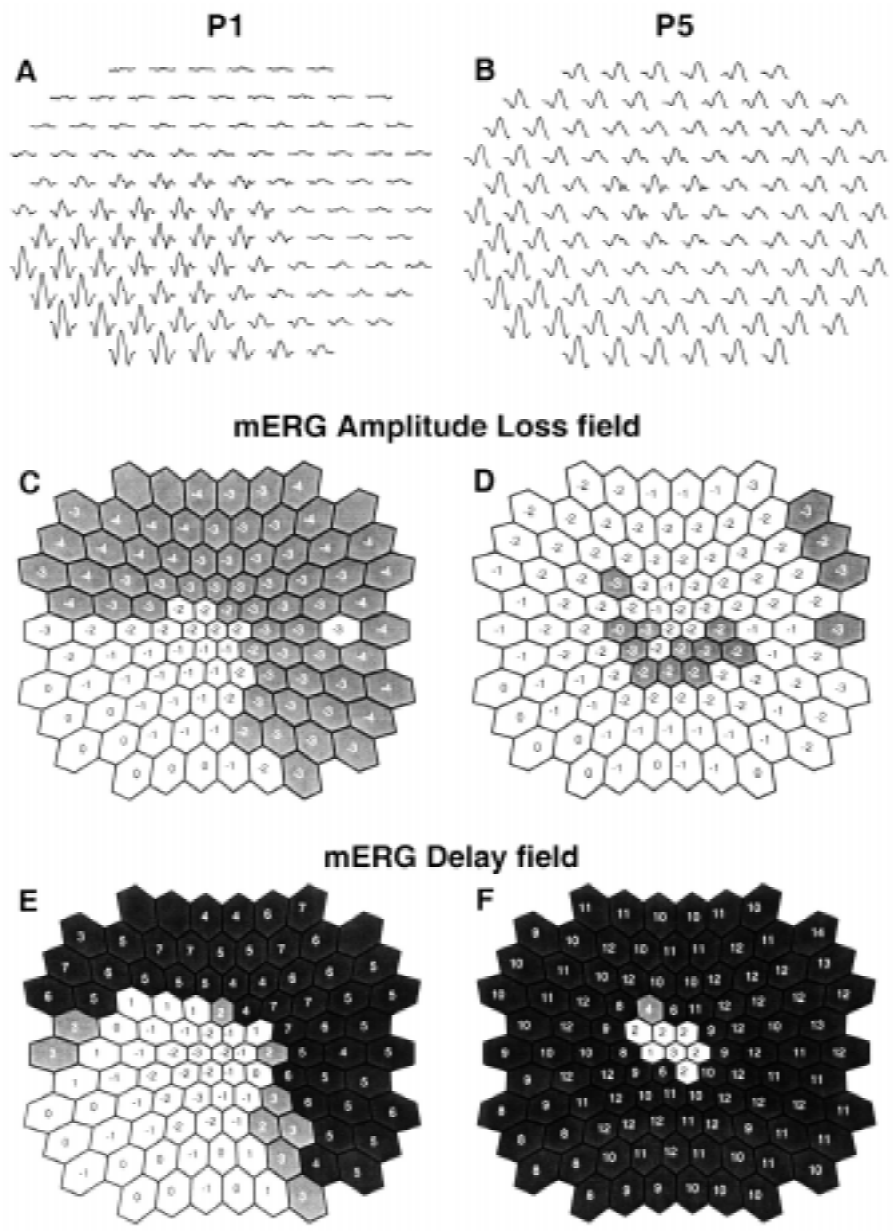

Figure 3. The mERG responses (panels A and B), the ERG Amplitude Loss Fields (panels C and D), and the ERG Delay Fields (panels D and E) are shown for two patients with RP. See [5] for details about the patients. The data here, however, were collected 3.5 years after the data presented in ref. [5]. The amplitudes and implicit times of the individual mERG responses were obtained as described in [6]. For the fields, white and dark signify values <2 s.d. and $>$ 4 s.d. from control values.

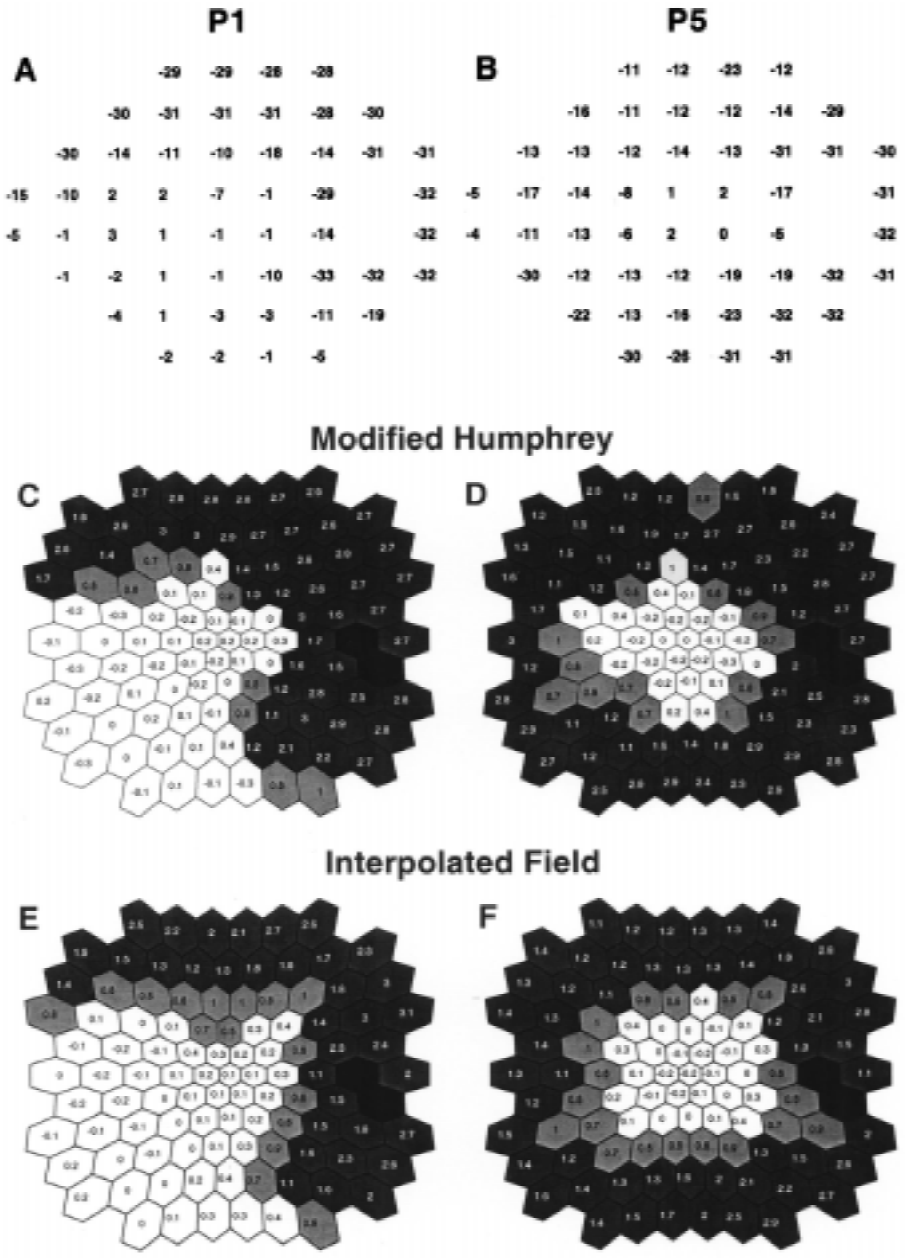

Figure 4. A, B: The 30-2 Humphrey total deviation fields are shown for the patients with RP (P1 and P5). C, D: Modified Humphrey fields. E, F. Interpolated fields.

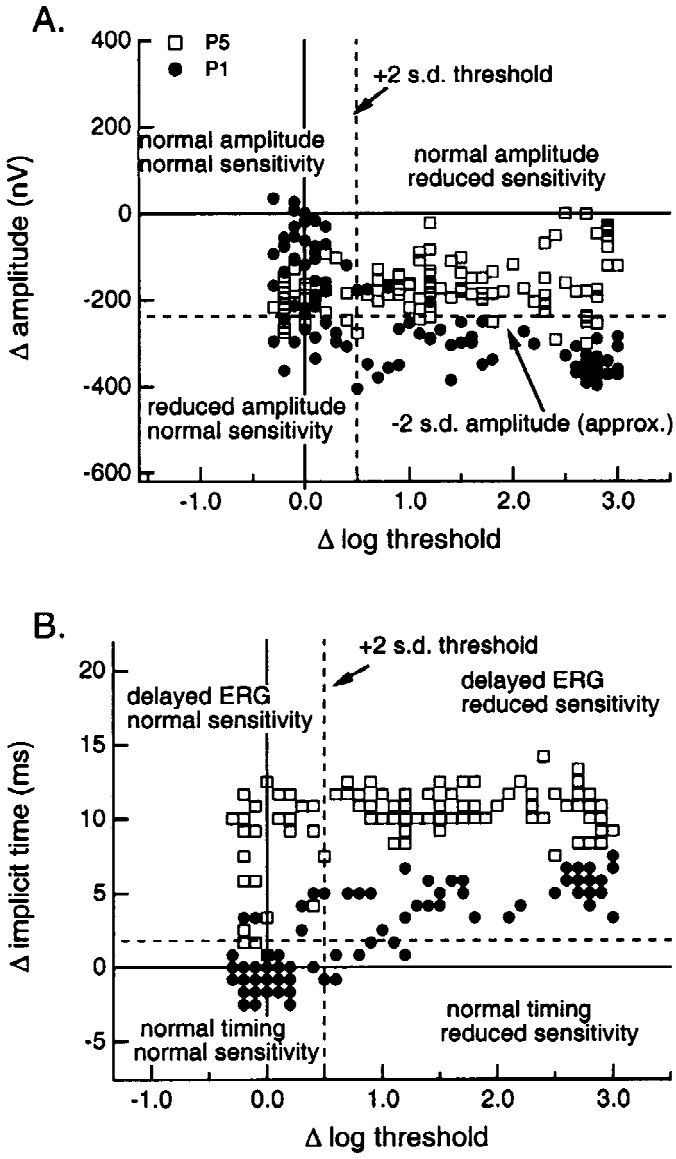

Figure 5. Amplitude loss (A) and delay (B) versus log threshold loss for the patients, P1 and P5, whose mERG responses are shown in Figure 3. The dashed lines show two standard deviations (s.d.) from the control group. This is an average s.d. as each hexagon location had its own s.d. value.

The modified Humphrey field. Older versions of the Humphrey Perimeter allows the user to specify the locations of the test spots. We have obtained Humphrey visual fields with the test spots placed in the centers of the hexagons employed for the mERG. Figure 4C, D shows these modified Humphrey fields for patients P1 and P5, coded in the same way as the mERG delay and amplitude fields in Figure 3. Now direct comparisons can be made. Amplitude loss does not correspond well with field loss, especially for P5. However, notice that, for both patients, there is reasonably good correspondence between the mERG delay field and the visual field. For P5, the region of near normal implicit times is smaller than the region of near normal field sensitivity. In our experience [5], this is a common finding and suggests that timing of the suprathreshold mERG is detecting early changes in these regions that are not yet apparent in the visual field. To quantify the relationship between the mERG fields and the visual field, the amplitude and implicit time for each location is plotted, in Figure 5, against the field threshold elevation. Notice that the correlation between the mERG amplitude and visual field loss is very poor. However, an abnormal field sensitivity is nearly always associated with a delayed implicit time. (In Figure 5B, nearly all the points that fall to the right of the vertical line fall above the horizontal line.) Further, if the implicit time is normal, the sensitivity will be normal. However, implicit time can be abnormal in regions of normal sensitivity, usually in regions that border on regions of abnormal sensitivity. (In Figure 5B, these are the points falling in the upper left-hand quadrant, 'delayed ERG/normal sensitivity'.) Based upon results like these, Hood et al. [5] concluded that the implicit time of the mERG is a better indicator of retinal health in patients with RP than mERG amplitude, and may well be better than field sensitivity as well.

The interpolated field. It is possible to estimate the sensitivity changes for the regions of the multifocal displays. Briefly, the points from the standard 24-2 or 30-2 (see Figure 4A, B) are used to obtain an estimate of sensitivity across the region covered by a hexagon or a sector in the multifocal array (see Methods). Figure 4E, F shows the interpolated field based upon the 30-2 data in Figure 4A, B. For comparison, Figure 4C, D contains the patient's modified Humphrey data obtained on the same day. By their nature, the interpolated fields will be less precise than the directly-measured modified Humphrey fields. However, given the ready availability of standard fields with equally spaced test locations (e.g. Tuebingen, Octopus and Humphrey), and given the reasonably close agreement between the interpolated and modified fields in Figure 4, this approach should prove useful.

Disease-related changes in fields and mERG responses

If a retinal disease depresses a region of the visual field, what can we expect the mERG to look like? The answer depends upon the site and mechanism of disease action.

Damage to the outer retina. Diseases that attack the cone receptor decrease the amplitude of the mERG response and depress local field sensitivity. According to a framework proposed by Hood [11], a disease that acts largely at the receptors will decrease the amplitude of the mERG and produce modest delays, up to 4–6 ms, in the implicit time of peak amplitude. The records from P1 (Figure 3A) fit this description. Stimuli falling in the abnormal region of P1's visual field (Figure 4C) produce small and moderately delayed mERG responses. In addition to RP [5, 6, 12, 13], other diseases that produce decreased amplitudes and moderately delayed responses include Stargardt's disease [14, 15] and AMD [15] (see ref [11] for other references and further discussion). However, some diseases that are thought to act primarily at the receptor can yield mERG responses that are reasonably large, but very delayed, in regions where the visual field is markedly depressed. The records from P5 (Figure 3B) fit this description. Stimuli falling in the abnormal region of P5's visual field (Figure 4D) elicit reasonably large, but very delayed (over 10 ms), mERG responses. Hood [11] argued that delays of 6 to 8 ms or more are too great to be due simply to outer segment changes (see also ref [16]) and are likely due to damage to the OPL, most probably at the synaptic connection between receptors and bipolars.

Damage to inner retina. Based upon the available literature, we have come to three conclusions about changes in the mERG secondary to damage of the inner retina [7, 11]. First, damage to the inner retina (i.e. amacrine cells, ganglion cells, and their connections) and/or optic nerve head can alter the mERG waveform, producing small changes in amplitude and timing. Second, however, when there are changes in the mERG waveform, due to inner retinal damage, they do not necessarily correlate well with local field losses. Third, damage to the ganglion cells, by itself, is not a sufficient condition to produce noticeable changes in the human mERG. Evidence for these conclusions can be seen in Figure 6, where the mERGs from the two eyes of patients with ganglion cell damage are compared. All three patients have more severe field losses in their left eye (see Figure 7). The mERG records for the patient P6 (OAG) with glaucoma and the patient P23 (ION) with unilateral ischemic optic neuritis are essentially identical in the two eyes, but the fields for the two eyes are very different (Figure 7). Evidence for the first and second conclusions above can be seen in the records from patient P14 (NTG) with

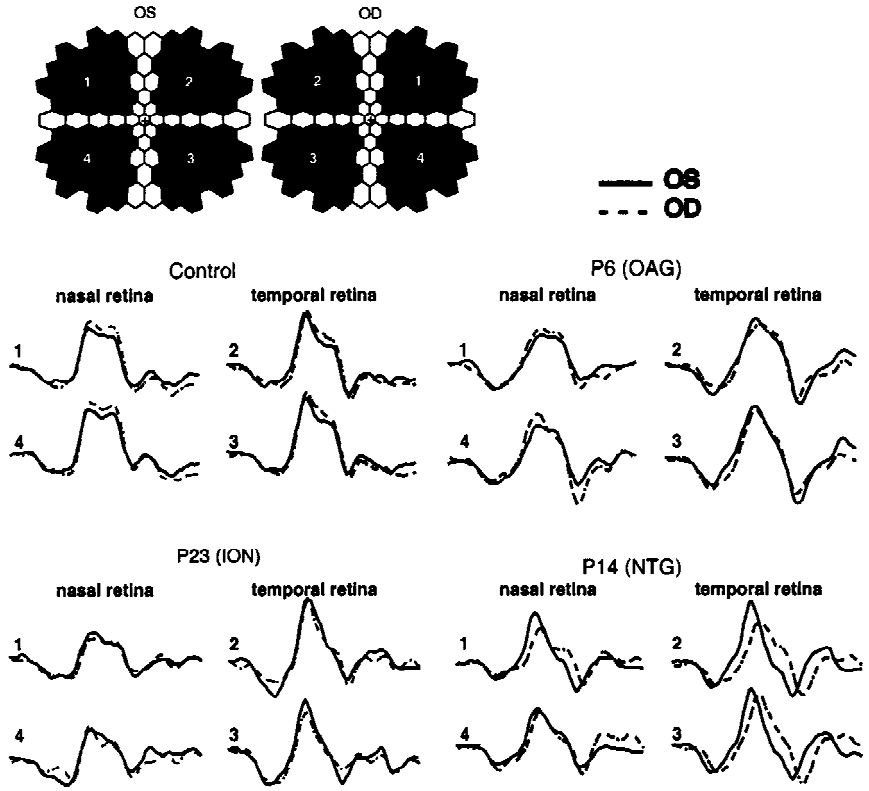

Figure 6. The mERGs from three patients and a control subject are summed within quadrants as shown. The 50% contrast display was employed [7, 9]. See [7] for details about the patients. The naso-temporal variations seen here are discussed in ref 9 and have a counterpart in the full-field ERG [17]. (Modified from figures in [7]).

glaucoma. Here the mERG responses from the two eyes differ but we could not find any evidence for a correlation between local changes in the mERG and local field changes [7].

The mVEP

Presenting mVEP measures as fields

The development of the mVEP has lagged behind the mERG. Although the mVEP was introduced in 1994 by Baseler, Sutter and colleagues [3], relatively little work has been done with patients until recently; the large inter-subject variability in mVEP responses has discouraged its use. In fact, in their pioneering study, Baseler et al. [3] concluded that clinical field testing would

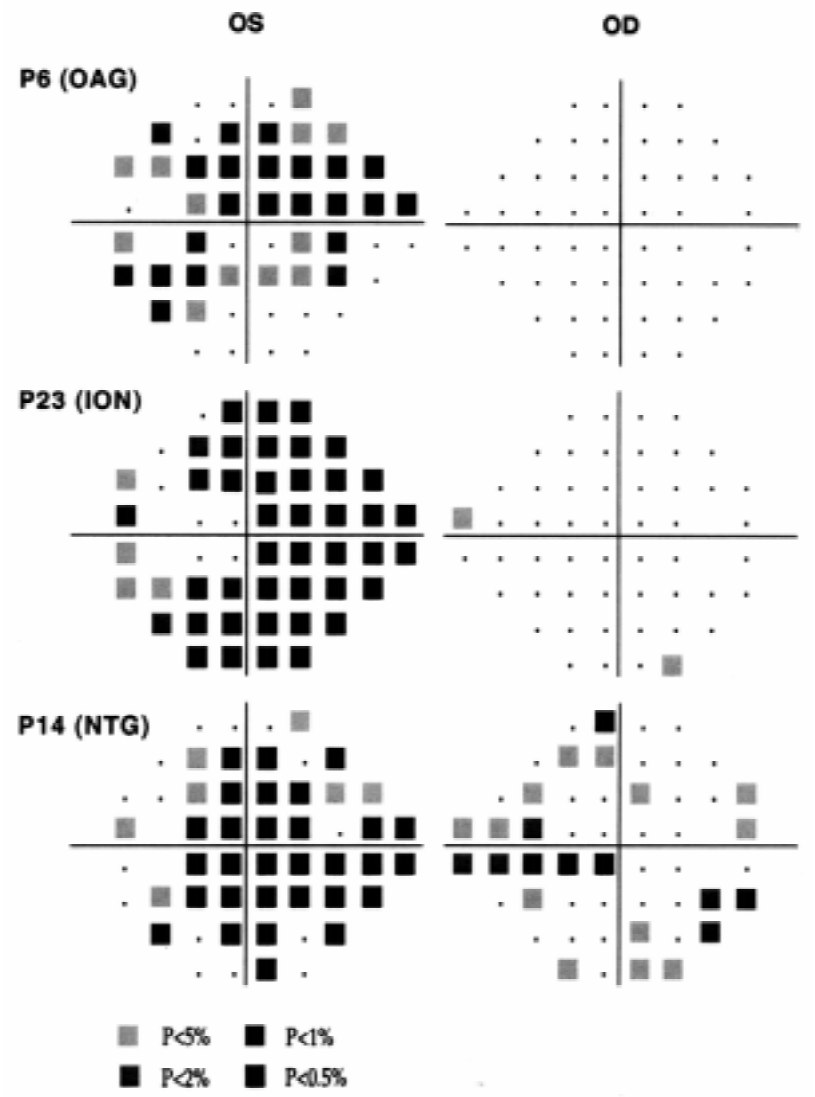

Figure 7. The 24-2 total deviation fields for the patients whose records appear in Figure 6. (Modified from figure in [8]).

not be feasible with the mVEP because there was too much inter-subject variability. In 1998, Klistorner, Graham, Grigg and Billson [18] concluded that, in spite of this variability, it was possible to see good correspondence between the mVEP and Humphrey visual field defects. Both studies observed that, with bipolar recording, the responses for stimulation of the upper and lower visual fields were reversed in polarity as expected from the anatomy of the

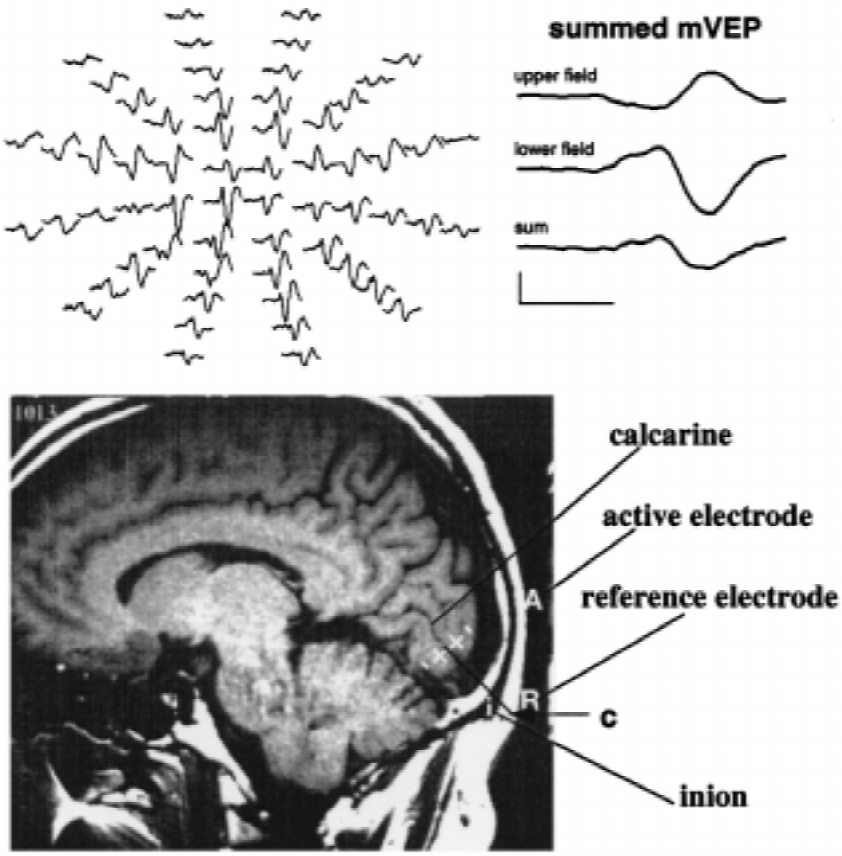

Figure 8. Mid-sagittal MRI showing the placement of the electrodes for the mVEP recordings shown in the upper left-hand panel. The summed responses for the upper and lower fields are shown in the upper right-hand panel. The calibration bars below the summed mVEP responses indicate 4 μV and 50 ms.

visual pathways (see Figure 8). More recently, Hood, Zhang, Greenstein et al. [8, 19] argued that, while inter-subject variability made it difficult to quantify visual field defects with the mVEP, this problem could be overcome by comparing monocular mVEP responses from both eyes of the same patient. (See also a study by Graham, Klistorner and colleagues [20].) Before describing this technique, let's consider the sources of inter-subject variability.

Inter-subject variability and the mVEP. There are two main sources of inter-subject variability. First, the position of the calcarine fissure relative to external landmarks varies among individuals [21]. Second, individuals differ in the way the cortex is folded and how the primary visual area is positioned within these folds [22, 23].

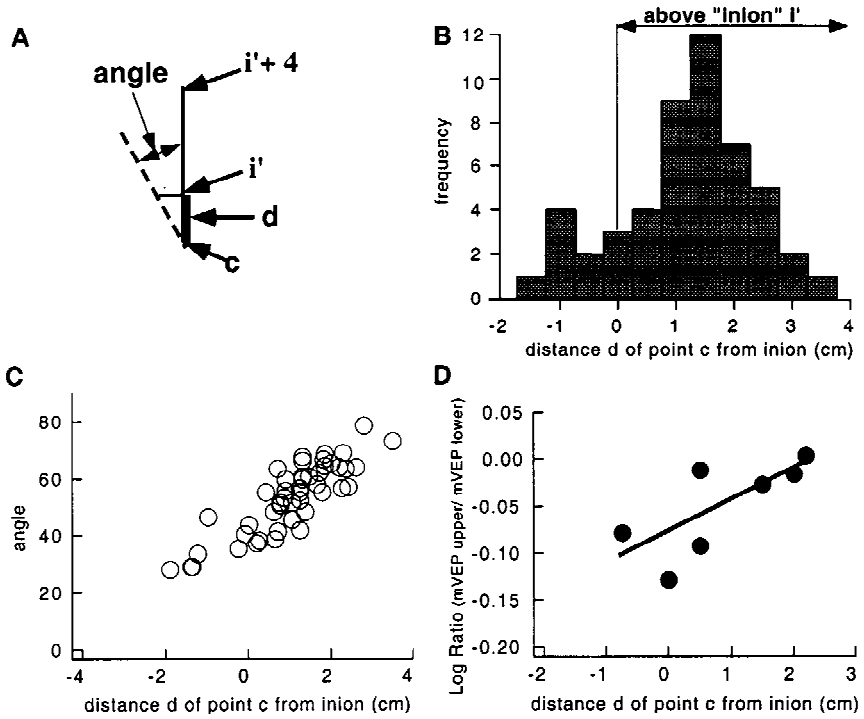

Figure 9. A: The dashed line indicates the line draw through the calcarine sulcus which intersects the skin at point c as indicated in Figure 8. The distance d between the point c and i′, the point on the skin corresponding to the inion, was measured in 50 individuals with normal MRI scans, as was the angle between the dashed line and a vertical line between the electrode positions. B: A histogram of distance d. C: The angle versus distance d. D: The mean ratio of the root-mean-square amplitudes of upper versus lower mVEP responses is shown as a function of distance d.

Our analysis argues that both sources, as expected, contribute to the inter-subject variability of the mVEP. Notice in Figure 8 that a line along the calcarine intersects the skin at point c. As described in the Methods and Figure 9A, the distance d between the point c and i', the point on the skin corresponding to the inion, was measured in 50 individuals with normal MRI scans. In addition, the angle the line through the calcarine sulcus made with the vertical line drawn between the electrode positions was also measured. The distance d varied from over 1.5 cm below to 3.5 cm above the inion (mean=0.95 above, s.d.=1.17) with 90 percent of the values falling between 1.25 cm below and 2.5 cm above the inion (see Figure 9B). The angle the calcarine sulcus makes with the vertical line between the electrodes varied from 30° to over 70° (mean=53.5°, s.d.=12.3) and this angle was highly correlated with distance d (see Figure 9C). As point c moves higher, the

calcarine sulcus becomes more perpendicular. Evidence that these variations affect the mVEP can be found in Figure 9D where the relative amplitude of the mVEP responses from upper versus lower field locations are shown for 7 subjects for whom we had both MRI scans and mVEP recordings. Notice that as point c moves higher, and the angle of the calcarine sulcus becomes more perpendicular, there is a tendency for the responses from the upper field (lower bank of calcarine) to become relatively larger. This is understandable in terms of the location and orientation of the cells in primary visual cortex (see Figure 8). These findings provide an explanation for two related observations. First, the responses from the majority of subjects are larger in the lower visual field (upper bank of calcarine) [3, 8, 18]. We found that in 29 out of 35 individuals the amplitude of the mVEP responses from the lower visual field were larger than those from the upper visual field. Second, the responses from the upper visual field in some individuals can increase in amplitude if the electrodes are lowered such that the reference falls below the inion [8, 18] as suggested by Klistorner et al. [18]. However, a major portion of the inter-subject variation is undoubtedly attributable to differences in cortical folding [22, 23]. The correlation (r=0.74) in Figure 9D is far from perfect. Further, individuals with similar positioning of the calcarine sulcus can have very different mVEP waveforms.

Two eyes are better than one. To circumvent the problem of inter-subject variability, the mVEP responses obtained from independent monocular stimulation of the left and right eyes can be compared [8]. If inter-subject variability is due to cranio-occipital variations, then the mVEP responses from the two eyes should be identical. The reason for this is purely anatomical; any point in the visual field projects to the nasal retina of one eye and the temporal retina of the other, but both points project to essentially the same region of striate cortex.

Figure 10 (top) shows the mVEP responses from monocular stimulation of the two eyes of the patient with glaucoma [P6 (OAG)] whose visual fields are shown in Figure 7. The mVEP responses from the two eyes of this patient differ, while the mERG responses (Figure 6) are nearly identical. For comparison to the mERG responses, the mVEP responses were summed across quadrants[1] for the same four individuals as in Figure 6, and are shown in Figure 11. Unlike the mERG, the summed mVEP responses in Figure 11 show clear differences between the two eyes of the patients, and these differences are in

[1] Although for these patients this serves our purpose, grouping by quadrants, in general, is not a good idea as the waveforms can differ within a quadrant. Hood et al. [8] describe a better way to group these responses.

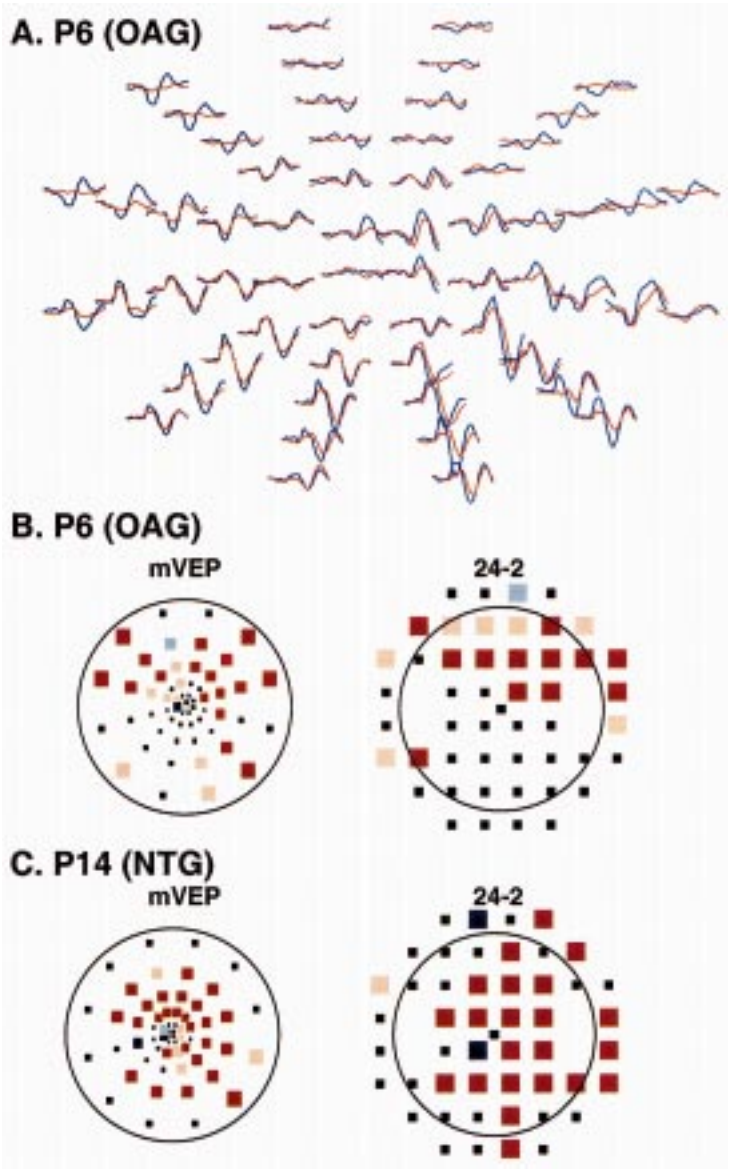

Figure 10. A: The mVEP responses from both eyes of P6 (OAG). B: The mVEP fields and 24-2 difference fields (OS-OD) for P6 (OAG). C: Same as in B, for P14 (NTG). (Modified from figures in [8]).

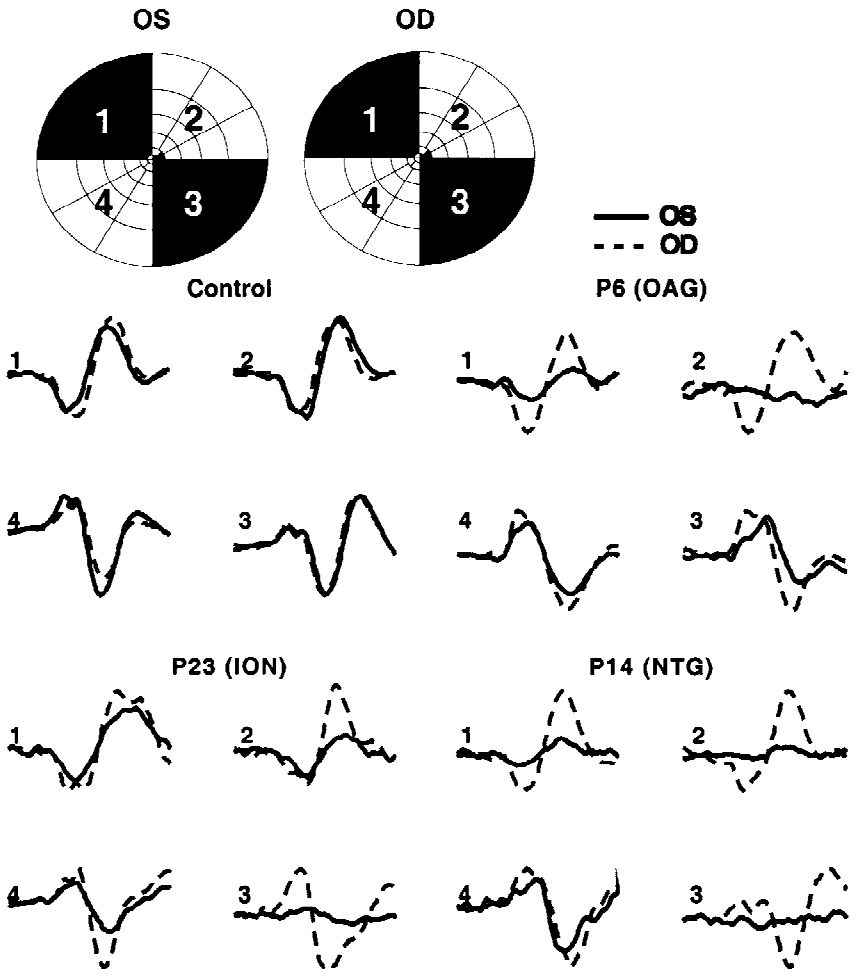

Figure 11. The mVEPs from three patients and a control subject are summed within quadrants as shown.

general agreement with the field changes (see Figure 7). [The agreement is easier to see with the interpolated fields discussed below (Figure 12).]

The mVEP field. The mVEP presents a more difficult problem than does the mERG because two eyes must be compared and because of the extreme scaling of the mVEP display, which is done to accommodate cortical magnification. Consider the visual fields (Figure 7) for patient P6 (OAG) whose mVEP records are in Figure 10 (top). How do we compare the visual fields to the mVEP when the scales are so different? To obtain a measure of the mVEP that can be presented in the same format as a visual field, we obtained the ratio

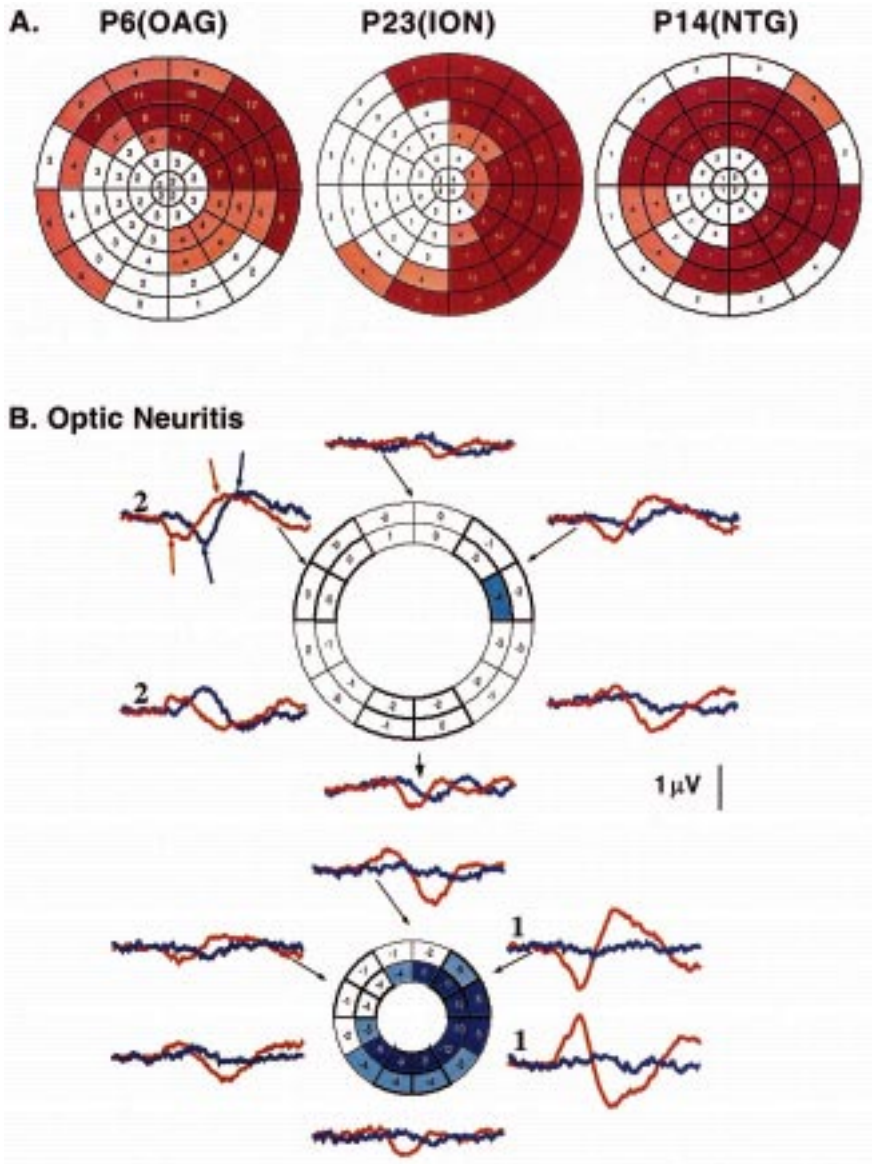

Figure 12. A: Difference visual fields interpolated from 24-2 Humphrey fields. B: Interpolated difference fields and mVEP responses from a patient who had an acute episode of unilateral optic neuritis 21 years earlier. This patient is described in ref. [8]. Each record is the sum of four mVEP responses as shown.

between the amplitudes of the responses from each eye [8], and compared it to the range of ratio values in a group of control subjects. [Technically, we used the log of the root-mean-square (RMS).] The details can be found in ref. [8] and are not important here. The important point is that for each pair of mVEP responses, one obtains a measure of one eye relative to the other. (For a different approach to comparing two eyes see ref [20].) The result of such an analysis for patient P6 (OAG) is shown in Figure 10B (mVEP field). Each square locates the center of one of the 60 sectors of the stimulus display. The black squares indicate that the response ratio was within 2 s.d. of the control values. The colored squares indicate that the response ratio was more than 2 s.d. (lighter desaturated color) or 3 s.d. (darker saturated color) from the mean of the controls. The color denotes whether the right (blue) or left (red) eye had the *smaller* response. (Note that the convention for color coding in Figure 10 for both the mVEP and 24-2 fields is the reverse of that in ref. [8] where the color coded the eye with the larger response.)

This mVEP field can be compared to the Humphrey visual fields. To make this comparison even easier, and more precise, the difference between the visual fields of the two eyes (Figure 7) was taken and is presented as a probability plot in Figure 10 (24-2 field, middle panel), on the same scale as the adjacent mVEP field [8]. Now the mVEP and 24-2 visual fields are in comparable forms, with the same linear dimensions. For the visual field, the color of the squares denotes whether the right (blue) or left (red) eye was *less* sensitive. For this patient, there is reasonable qualitative agreement. The left eye has the lower sensitivity and the smaller responses. The two blue locations on the mVEP field indicate smaller responses for the *right* eye; the eye with the better overall field sensitivity. These could be false positives but the central location replicated on a subsequent visit and is probably an example of the mVEP showing a defect not readily detectable by the visual field. Figure 10C contains the same analysis for P14. The blue points in this patient's mVEP field indicate regions where the mVEP is identifying a very subtle difference between the two eyes (see Figure 7 in [8]).

A comparison of mVEP and perimetric fields

Quantitative comparison: interpolated fields. Interpolated fields (see Methods) can be estimated for the mVEP display as was done for the mERG display, in Figure 4. Figure 12A shows these fields for the three patients whose records are in Figure 11. Unlike the fields for the mERG, these are not presented on linear coordinates, as it would make the central regions impossible to discern. Rather they are shown in a fashion similar to the mVEP response displays. Also, like the fields in Figure 10, these fields show the *difference* between the two eyes. For a quantitative comparison, scatter plots,

similar to those in Figure 5 for the mERG, can be obtained relating the local estimates of field loss in the interpolated field to the mVEP amplitude measures underlying Figure 10 [24,25].

Qualitative comparison. The interpolated field is also useful for making a more qualitative comparison between the mVEP and field changes. Figure 12B shows the interpolated field for a patient who had an episode of acute, unilateral optic neuritis 21 years earlier. The upper set of records in Figure 12B shows the mVEP summed across groups of four mVEP responses around the outer two rings and the lower set shows a similar grouping around the next two inner rings. The mVEP responses are smaller in the affected eye in the regions of abnormal sensitivity (e.g. those labeled 1). Further, in some regions of normal sensitivity the responses from the affected eye are of normal amplitude but very delayed (e.g. those labeled 2). We have recently shown that such regions with normal field sensitivity but delayed mVEP responses are associated with regions that showed visual field defects during the acute phase [9, 26].

Disease-related changes in fields and mVEP responses

Compared to the mERG, relatively less is known about the relationship between disease-related changes in fields and mVEP responses. It is clear that local damage to the ganglion cell and/or optic tract decreases the amplitude of the mVEP [8, 18]. The decrease in amplitude is correlated with the degree of field loss in patients with ION and glaucoma [24, 25]. On the other hand, implicit time changes are not very impressive in these patients and do not correlate well with field loss [24, 25]. The relationship between the field sensitivity and the amplitude or implicit time of the mVEP is different in the case of the patients with optic neuritis (Figure 12). At the onset of optic neuritis, both amplitude and implicit time changes are associated with regions of field loss. With time, although any residual field loss will still be associated with a decrease in mVEP amplitude, increased implicit time correlates with the visual field obtained at onset, but not necessarily with the concurrent field [8, 9, 24, 26].

Summary

Although the spatial format of the visual field and the multifocal array differ, the data from the two techniques can be compared. Here, various approaches for comparing these data were presented. The best approach to use will depend upon the question to be answered. We emphasized above that the two

techniques need not agree. In fact, it may well be that the points of disagreements are the most informative. For example, the large mERG responses found in regions of poor sensitivity in some patients with RP, but not in others, suggest different mechanisms of damage. And, the markedly delayed mVEP responses in patients with optic neuritis in regions of normal field sensitivity seem to locate previously abnormal fields. In any case, it is clear that there is new information to be had by comparing visual fields and multifocal responses.

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