

The Multifocal Electrophoretogram (mfERG): Applications and Limitations

Donald C. Hood, Ph.D.

New York, NY

Objective

To review the multifocal visual electrophoretogram (mfERG) technique and to illustrate its use in neuro-ophthalmology.

Method

The mfERG was recorded with a bipolar Burian-Allen contact lens electrode after the pupil was dilated with 1% tropicamide. The display, 50° in diameter, consisted of 103-scaled hexagons. One 8-min. run was recorded per eye. Amplitudes and latencies were examined with the VERIS software from EDI. Achromatic automated visual fields (Humphrey program 24-2) were obtained for all patients.

Results

Four applications of the mfERG were identified. The mfERG was valuable for ruling out the retina as the site of disease; distinguishing among diseases; ruling out functional or nonorganic causes; and following the progression of a retinal disease.

Conclusion

When combined with static visual fields, the mfERG aids in the diagnosis and the planning of treatment for patients seen by the neuro-ophthalmologist. Of particular importance is the mfERG's ability to distinguish diseases of the retina (pre-ganglion cells) from diseases of the ganglion cells and the optic nerve.

What Is the mfERG?

The electrophoretogram (ERG) is a mass potential, the result of the summed electrical activity of the cells of the retina. Typically, the clinical ERG is elicited by full-field (Ganzfeld) flashes of light. With an appropriate selection of test and background lights, rod and cone function can be assessed separately.¹ As the ganglion cells contribute relatively little to the full-field, flash ERG, the ERG has helped neuro-ophthalmologists to distinguish between diseases of the retina (i.e., before the ganglion cells) and diseases of the ganglion cells or optic nerve. However, because the ERG is the sum of all retinal activity, relatively large retinal defects can go undetected by standard full-field ERG testing. While both the pattern ERG and focal ERG can provide information about losses in the foveal region [e.g., ^{2,3}], these techniques do not provide topographical information.

The multifocal ERG (mfERG) technique was developed by Sutter and colleagues to provide a topographical

measure of retinal activity.⁴⁻⁶ With the multifocal technique, 100 or more focal ERG responses can be recorded from the cone-driven retina in 8 minutes. Although this technique is relatively new, it has been used widely to diagnose and study retinal diseases. (See ref. 7 for a review.) In the current review, the mfERG technique is described and applications in neuro-ophthalmology are discussed. We argue that, when combined with static, automated perimetry, the mfERG is a valuable tool for the neuro-ophthalmologist.

How Is the mfERG Recorded?

The Display

Figure 1A, B shows the mfERG display employed in the work summarized here. This display is similar to the one originally described by Sutter and Tran⁵ and is a standard part of the VERIS software (EDI, San Mateo) developed by Sutter.^{4-6,8} The display used for the work described here consisted of 103-scaled hexagons and subtended about 50° in diameter when viewed at 32 cm. The hexagons were scaled to produce approximately equal size ERG responses from individuals with normal retinal function.⁵ For example, the central most sector is about 3° wide while the outermost sectors exceed 7°. For clinical purposes, some have used a display of 61 hexagons which produces larger responses but poorer spatial resolution.

The white hexagons were 200 cd/m² and the black hexagons the darkest the screen allowed, about 5 cd/m². The area surrounding the array of hexagons was set to 100 cd/m² and a central cross was used for fixation. All recordings were performed with the room lights on to help assure a constant state of light adaptation. Because of the light levels employed and the rapid rate of stimulation, the mfERG is a response of the cone system.

Recording the Signal

In general, the mfERG signal is recorded with the same electrodes and amplifiers employed for conventional ERG recording. The critical differences are the display, the method of stimulation, and the analysis of the raw records. For the records shown here, a single continuous ERG record was obtained with a Burian-Allen contact lens electrode, although a variety of electrode types can be used. The most commonly used noncontact lens electrode is the DTL.⁹ The contact lens electrode is less comfortable to wear, but yields superior records. Although it is possible to analyze records offline (e.g., ¹⁰⁻¹²), all the analyses shown here were done with the VERIS software.

From a single, continuous ERG signal (Fig. 1D), the software extracts 103 mfERG responses, each associated with one of the sectors of the display (Fig. 1E). That is, 103 responses are obtained from a single record. To get a sense of how this is possible, the nature of the local stimulation of each sector must be examined.

Stimulation and Extracting the Local Responses

To understand the mfERG technique, it is essential to understand how each of the sectors is varied during the test. Each sector is an independent stimulus. Every 13.3 ms the frame of the monitor changes and each sector has a 50/50 chance of appearing “white” (briefly flashed) or “black” (no flash). Figure 1C shows a series of frame changes for two of the locations. Each of the 103 sectors of the display in Fig. 1A, B goes through its own pseudorandom sequence. In fact, the 103 pseudorandom sequences are the same series of “white” or “black,” but the sequence for each of the hexagons starts at a different point in the series. The reason for this, and the nature of the pseudorandom series, are technical details that are not necessary to understand. It is sufficient to know that these pseudorandom sequences allow the software to rapidly extract the response associated with each of the 103 hexagons.⁴ [The reader who is interested in learning more about the technical details should consult refs. 4-8.]

Figure 2A provides a nontechnical explanation of how it is possible to extract 103 responses from a single record. Suppose you summed the first 60 ms of the record following all the frames at which a particular hexagon appeared white. It would look something like the response R in Fig. 2A. Likewise suppose you summed all the records following each frame on which the same hexagon appeared black. It would look something like NR in Fig. 2A. Response R should contain the responses to all the hexagons that flashed (appeared white), including the hexagon in question. The response NR, on the other hand, will include the responses to all the hexagons except the hexagon in question. The difference between R and NR is the response to the hexagon in question. These responses (e.g., Fig. 1E) are called first-order kernels. [For a more realistic picture of the waveforms underlying the first-order kernel see Fig. 27 in ref. 7.] While the software could in principle calculate the 103 mfERG kernels or responses this way, it does not. Technically, each mfERG response (Fig. 1E) is the result of a serial correlation between the stimulation sequence of a particular hexagon (Fig. 1C) and the single continuous ERG record (Fig. 1D). A pseudorandom sequence chosen in a certain way (so-called m-sequence) coupled with a special algorithm allows the software to make these calculations very quickly.⁴

Displaying the Responses

Figure 1E shows the 103 mfERG responses for stimulation of a right eye from a normal subject. These responses are positioned so that they do not overlap and thus the scaling is arbitrary as a comparison of the circles in Figs. 1A and E indicates. We find the trace array in Fig. 1E to be the most useful presentation of the data. In some cases, it is helpful to sum or average the responses within various regions of the display. Often responses are summed within rings around fixation. In Fig. 3B, the responses from Fig. 1E are grouped by rings around fixation (see Fig. 3A) and summed. The responses become larger with eccentricity because progressively larger areas of the retina are stimulated. To take area into consideration, the amplitude of the summed response is divided by the total area of the hexagons in that ring. The resulting responses (Fig. 3C) are expressed in a measure of response amplitude per unit area or response density (nV/deg²). As expected, the response per unit area is highest in the fovea.⁵ Although this analysis by rings is useful for many purposes, it is not an appropriate display for summarizing the effects of retinal diseases that have naso-temporal asymmetries. It also obscures the naso-temporal differences that are present in the normal mfERG.^{7, 12} The software available to analyze the mfERG, however, allows for the combination of responses from any arbitrary grouping of hexagons (e.g., Figs. 8, 12 and 13).

The mfERG results are often displayed in a 3D plot. Figure 1A (bottom) shows the results from Fig. 1E as a 3D plot. To obtain this display, the response amplitude is divided by the area of the hexagon (i.e., the response density is obtained for each hexagon). There is a depression and a peak associated with the optic disk and the fovea, respectively. Although the 3D plot is pleasing to the eye, it can be very misleading (see below). The 3D plot should never be published, or analyzed, without the associated trace array.

Relation to Conventional ERG and Cellular Components

As typically recorded, the mfERG is from the central 25° (radius) of the retina (Fig. 1A). The display covers only about 25% of the cone photoreceptor cells.¹³ Further, the high rate of stimulation, combined with the light levels employed, assures that the rods do not contribute except under very unusual circumstances.^{14, 15} Like the traditional photopic, or cone-driven, ERG, the mfERG shows an initial negative component (N1) followed by a positive component (P1) (e.g., see Fig. 3C). These components bear a superficial resemblance to the a- and b-waves of the photopic, flash ERG. However, the waveform of the mfERG differs from that of the typical, photopic ERG.^{7, 13}

This is not surprising as both the stimulus and the analysis are different. Recall that the standard, full-field ERG is the sum of one or more responses to single flashes. In contrast, the mfERG is not a response at all, but rather a mathematical extraction (see Fig. 2A). Thus, the components of the mfERG should never be referred to as a- and b-waves.¹

In spite of these differences, it appears that N1 is composed of the same components as the a-wave of the full-field ERG and P1 is composed of the same components as the positive waves (b-wave and OPs).^{7, 13} As in the case of the full-field ERG (e.g.,^{16, 17}), the mfERG waveform is largely shaped by bipolar cell activity with smaller contributions from the photoreceptor cells and inner retinal cells (e.g., amacrine and ganglion).¹⁸ Figure 4 shows Hood et al.'s model of how the cells of the outer retina contribute to produce the mfERG waveform.¹⁸ The N1, P1, and N2 components are influenced in different ways by the onset and offset of the bipolars and to a much lesser extent by the receptors. In addition, inner retinal influences exert subtle influences on the waveform. For example, in the monkey, the "ledge" on the trailing edge of P1 is removed by blocking the action potentials from the amacrine and/or ganglion cells.¹⁸⁻²⁰

The analysis of the components of the mfERG (Fig. 4) contains an important message. Only damage at or before the bipolar cells will substantially decrease the amplitude of the mfERG. Inner retinal damage to amacrine and/or ganglion cells can affect the waveform of the human mfERG (e.g.,^{19, 21-24}). However, these effects are subtle and do not include a significant decrease in the amplitude of the mfERG. As an example, Fig. 5 shows the mfERGs recorded 8 months after the occurrence of ischemic optic neuropathy (ION). The responses have been summed within each quadrant for each eye. Although there is extensive ganglion cell damage, the mfERGs from the affected eye are similar to those from the unaffected eye.

Applications

Over the last 4 years, we have been routinely recording mfERGs from patients seen by two neuro-ophthalmologists, Drs. Myles M. Behrens and Jeffrey G. Odel. Here we summarize our experience with the mfERG as a diagnostic tool by grouping the patients into the most common reasons for seeking a mfERG.

Rule Out Retina

The neuro-ophthalmologist is routinely faced with deciding whether a visual defect has a retinal (before the ganglion cells) or post-retinal (at the ganglion cell/ optic nerve or beyond) basis. The mfERG can be very helpful, especially in situations where standard tests provide ambiguous information. Since damage to the ganglion

cells or optic nerve does not decrease the amplitude of the mfERG, an abnormal mfERG provides strong evidence for a retinal basis. Below we provide examples.

Patient 1 is a 16 year old female with a 1 year history of difficulty reading, especially with her left eye. Her visual acuity was 20/25-2 (OD) and 20/60-1 (OS). She was referred to a retinal specialist who found that the full-field ERG was normal and questioned whether optic neuritis was the cause of her problem. Her mfERGs in Fig. 6B clearly suggest a retinal basis. However, it is essential to compare the mfERG findings to the visual fields from static perimetry. Normal variations, as well as various artifacts (see below) can produce mfERG responses that may be smaller than normal. To help avoid these problems, we compare the mfERG results to visual fields from static, automated perimetry. Patient 1's 24-2 Humphrey visual fields (HVF) are shown in Fig. 6A. To help in the comparison of the HVF to the mfERG topographies, iso-degree contours have been added as shown by the circles in color. While more sophisticated procedures for comparing the HVF to the mfERG exist (e.g. 25), these contours are sufficient for most clinical purposes. The records in Fig. 6C show the mfERG responses (in response density) within the central 5° (red), between 5° and 15° (blue), and between 15° and 25° (green). [These are equivalent to center & ring 1, rings 2-4, and rings 5 & 6 in Fig. 3.] The agreement between the depressed amplitude of the mfERG (Fig. 6B) and the regions of the HVF defects (Fig. 6A) confirmed that the problem is retinal in origin. The mfERG, reduced in amplitude but relatively unchanged in implicit time, resembles those seen in Stargardt's disease [e.g.,²⁶].

Patient 1 illustrates a problem often facing the neuro-ophthalmologist, namely, differentiating optic nerve from retinal dysfunction in patients with an unexplained loss of central vision and a normal fundus exam. In some cases, the unexplained loss can be paracentral as in the case of Patient 2. Patient 2 is a 41 year old male engineer with a 4 month complaint that his vision OS resembled a "smudge" on his glasses; he had no complaints OD. His fundus appeared normal and his visual acuity was 20/20. His 24-2 HVFs (Fig. 7A), however, showed paracentral ring scotomas OU. Both glaucoma and a retinopathy were possible diagnoses. The problem is clearly retinal, as the mfERG was depressed in regions corresponding to his field defects. He was later shown to have abnormal antibody activity suggestive of Melanoma Associated Retinopathy (MAR). This type of defect would be hard to detect with either the traditional full-field or focal ERGs.

The next patient illustrates how the mfERG can detect relatively local changes that would surely be missed with other ERG methods including the focal ERG. Patient 3, a

58 year old female, had a 10 year history of episodic flashing in both eyes, most often in the right eye, suspected of being migrainous in nature. Several weeks prior to her visit, the flashes seemed different and appeared only in the superior temporal field of the right eye in the region corresponding to the defect seen on her HVF (Fig. 8A). Her fundus appeared normal except for mild irregular narrowing of the branch retinal artery in the region of the defect. The subtle change in the amplitude of the mfERG responses in the region of the defect (Fig. 8B) combined with the narrowed artery suggested branch retinal artery occlusion (BRAO). Localized defects are sometimes easier to visualize in the 3D plot (Fig. 8D) and in the second-order kernel array (Fig. 8C).²⁷ (The second-order kernel will be discussed below.)

Distinguishing Among Diseases

With the mfERG, it is often possible to distinguish among different retinal diseases. In particular, changes in the relative amplitudes and latencies of N1 and P1 can provide a clue as to the site and mechanism of the disease process. A complete discussion of this topic is beyond the scope of this presentation. (See Table 1 in ref. 7 for a review.) However, it is important to take note of the latency of the P1 peak of the mfERG. A large delay in the timing of the mfERG is associated with damage to the receptors/outer plexiform layer.⁷ Damage to the inner nuclear layer (e.g., bipolars) and beyond yields relatively small changes in the implicit time of P1 and may even shorten it. Patient 4, a 62 year old male, had a long history of difficulty with reading, but only mildly reduced acuity (20/20 OD; 20/40 OS). His retinal evaluations, including angiograms, were normal. His visual fields showed bilateral central scotomas. The left panel of Fig. 9A shows the 10-2 HVF for his left eye. Because of the nature of his visual fields and a normal appearing fundus, he underwent repeated and extensive neuroradiological, neurosurgical, neurological, and serological examinations. They were all normal. The mfERG (Fig. 9A-right panel) showed reduced amplitudes in the central 5° and delayed implicit times at all locations including those where the Humphrey visual fields were normal. The delays can be seen more easily in Fig. 10 where the first 40 ms of the responses are shown for this patient (Fig. 10A) and for a normal subject (Fig. 10B). Delays such as these are seen in cone dystrophies²⁸ and retinitis pigmentosa^{29, 30} and are associated with damage to the receptors/outer plexiform layer.⁷ Patient 4's findings fit the definition of occult macular dystrophy (OMD) proposed by Miyake and colleagues. Typically these patients present with normal or mildly to moderately reduced acuity, normal peripheral fields, small central or paracentral defects, and normal or only mildly

abnormal full-field ERGs. They are best diagnosed with focal or multifocal ERGs.

Patient 5 provides another example where a delayed mfERG suggested a degenerative condition of the receptors. A 48 year old female presented with blurred vision and a 6 month history of flashing lights OU. Her visual acuity was 20/20 OU, her color vision (D15) was normal and her 24-2 visual fields were constricted OU. Figure 11A shows the HVF for her left eye obtained on 1/5/00. Her fundus exam showed a waxy pallor of disc, mild arterial narrowing, some inner limiting membrane changes over macula, RPE thinning, and vitreous cells. A mfERG was performed to confirm a retinal diagnosis and to see if some clue could be found as to the cause. Her mfERG is shown in Fig. 11B. At first glance these are not very impressive given her field defect. However, although the amplitudes are reasonably good, the responses from the affected region of the field are very delayed. This can be seen in Fig. 10 where the first 40 ms of the responses are shown for this patient (Fig. 10C) and for a normal subject (Fig. 10B). The mfERGs are delayed in all regions of the field except for the central region. Further, the region of the delays corresponds to the abnormalities in the field as can be seen by comparing Figs. 11A and 10C. This pattern is seen with diseases of the receptors and pigment epithelium such as RP and cone-rod dystrophy.^{7, 28-30} Although we initially thought that the patient's problem was RP, her vision continued to deteriorate at a rate far too fast for RP. Figure 11C and D shows her HVF and mfERG obtained 15 months later. The field has constricted and the mfERG amplitudes have markedly decreased in the region previously showing the delays. Although this rate of decline makes RP unlikely, the problem may well still be at the receptors and/or pigment epithelium. She was subsequently found to have antibodies to all levels of the retina (Dr. Charles Thirkell, personal communication) and her RPE showed a particularly marked hypersensitivity on a test using RPE cells grown in tissue culture.³¹

The neuro-ophthalmologist is often faced with a patient with two diseases, each of which could, in principle, explain the patient's visual loss. Although in these cases, distinguishing between diseases is often a case of ruling out the retina as discussed above, two examples are worth considering here as they illustrate other points as well. Patient 6, a 43 year old male, was a former Olympic soccer player whose MRI showed a third ventricle tumor adjacent to the anterior visual pathway. A nasal scotoma OD was found on visual field testing. His visual acuity was 20/20 OU and his fundus exam OD revealed a region of hyperpigmentation in the temporal retina. A mfERG was obtained to determine whether the tumor was the cause of the defect. There is a local decrease in the mfERG OD in the region of the

scotoma. This is best seen by comparing the responses from the two eyes. Since there are naso-temporal variations in the mfERG that can be quite large in some individuals, it is important to compare responses from corresponding regions of the retina of the other eye in the case of small unilateral lesions. The responses from the left eye (red) are reversed in Fig. 12. The mfERG is smaller in the region of the defect. The tumor was not the cause of the scotoma. Rather, this patient's visual field defect was more likely due to a retinal injury as supported by the hyperpigmentation in the fundus.

Figure 13 shows another example where there were two preexisting conditions, each of which could have caused a field defect. Patient 7 is a 61 year old female with a history of a left-sided branch retinal vein occlusion (BRVO) three years prior to presenting for investigation of her visual field defect OS (Fig. 13). Her visual acuity was slightly reduced OS (20/30) and her IOP (16 mm Hg) was normal. There was probable disc excavation OS. Her mfERG was normal in the region of the visual field defect (see green rectangle in Fig. 13). Thus, normal tension glaucoma is the likely cause of this defect. Notice, however, that there is a small decrease in the mfERG amplitudes in the macula corresponding to macular edema secondary to the old BRVO (magenta circle).

Follow Progression

The mfERG shows good repeat reliability^{32, 33} thus it can be used to follow the progression of a disease. While this is particularly helpful in the case of patients who are poor field takers, it can be of value in other cases as well. Patient 5 (Fig. 11) illustrates one example. The marked change in the mfERG over a 15 month period suggested that our initial impression that this patient had RP might be wrong. The field and the mfERG progressed more rapidly than one would expect for RP. Given the evidence of retinal antibodies mentioned above, an autoimmune process is suspected.

Rule Out Functional or Nonorganic Causes

The mfERG can be used to rule out functional (nonorganic) causes. The advantage of the mfERG over the conventional ERG is that it provides a topographical representation that can be compared to the patient's visual fields. Figure 9B illustrates this point. Patient 8 is a 30 year old police officer who complained of decreased vision OS for the last few years, especially during the day. A nonorganic cause was considered. The mfERG shows depressed responses in the macula (Fig. 9B-right panel). This prompted indocyanine green (ICG) angiography and optical coherence tomography (OCT) that suggested a resolved central serous chorioretinopathy.

While an abnormal mfERG can be used to rule out a functional cause, a normal mfERG does not mean that the problem is functional. If the mfERG is normal, then a multifocal VEP should be performed as well to rule out damage to the optic nerve/ganglion cells.³⁴

Advanced Topics

What is the second-order kernel and where does it come from?

It is important to have some understanding of the second-order kernel or response (2K) as some investigators have claimed diseases of the ganglion cell/optic nerve affect it differentially. Like all the multifocal responses, it is not, technically speaking, a response. It is a mathematical extraction. Figure 2B provides a simple way to understand the meaning of the 2K. The flashes in Fig. 2A that make up the first-order response (1K) can be divided into two groups. Half of the times that a particular hexagon appeared white, a flash preceded it (small white hexagon in Fig. 2B). For the other half of the times, a flash did not precede it (small black hexagon in Fig. 2B). If the responses under the two conditions are the same, then there is no 2K. If these two responses differ, then there is a 2K and it is the difference between the 1K responses. Thus, the presence of a 2K indicates that there is an effect of short-term adaptation. In the normal mfERG, the presence of the flash on the preceding frame makes the response slightly smaller and slightly faster. Thus, the shape of the 2K is complex, as indicated in Fig. 2B.

Some investigators speak as if the 2K is an actual response generated in the inner retina, some even say by the ganglion cells. As the discussion above indicates, the 2K is not a response and thus strictly speaking can not be generated anywhere. We do know that blocking action potentials generated by the ganglion cells and amacrine cells in monkeys markedly reduces, but does not eliminate, the 2K.¹⁸ On the other hand, although ganglion cell damage can reduce the 2K in humans,²¹ a large 2K can be present even with extensive damage.²² Therefore, it appears that inner retinal damage, but not necessarily ganglion cell damage, can decrease the 2K in humans. However, outer plexiform damage can completely eliminate the 2K in patients with degenerative diseases of the receptors or, in some cases, diabetic retinopathy.⁷ Consequently, it is a mistake to associate a diminished 2K with damage of a particular set of cells. A diminished 2K indicates an abnormality in the circuits and connections involved in adaptation rather than a missing component or cellular response.⁷

The 2K can be useful, however, in identifying local lesions of the inner nuclear layer and/or receptors. As mentioned above, the 2K is reduced more than the 1K by BRAO.²⁷ This can be seen in Fig. 8 where the 2K

responses are reduced more than the 1K. Although the selective loss of the 2K has been interpreted as an indication of inner retinal damage, it is more likely due to a reduced effect of stray light²⁷ and/or damage at the outer plexiform layer.⁷ For example, Shimada and Horiguchi³⁵ have shown that the spatial resolution of the 2K is better than the 1K because the 2K has a smaller contribution from stray light.

Other Paradigms

The software available for creating the display and for modulating the temporal sequence of light presentations allows for a wide range of spatial and temporal paradigms. A number of paradigms have been developed to help detect damage to the inner retina (i.e., amacrine and ganglion cells) (e.g., ³⁶⁻⁴¹). The best developed of these is the global flash paradigm.³⁶ This paradigm is designed to accentuate a component generated at the optic nerve head (ONH) by action potentials from ganglion cells. The existence of an ONH component has been fairly well established^{20, 21} and there is some evidence that glaucoma can eliminate it.³⁶ However, the ONH component is small and its usefulness in detecting glaucomatous damage uncertain.⁴¹ Until more evidence is presented that one or more of these new paradigms can detect damage to the ganglion cell, we do not recommend using the mfERG to study diseases of the ganglion cell/optic nerve. If an electrophysiological measure of ganglion cell/optic nerve is needed, the multifocal VEP is a better candidate (see refs. 34 and 42 for a review).

Some Limitations

Eccentric Fixation

As in the case of visual field testing, it is important to monitor the patient's eye position. An eye camera or direct visualization of the eye should be used to assure that fixation is steady. Unsteady fixation can cause diminished responses in the center of the field. Monitoring the eye, however, will not assure that the fixation is accurate. Some patients with central visual problems can have eccentric fixation and eccentric fixation will produce mfERGs that appear to have central and paracentral defects. Figure 14 illustrates this point. Figure 14C contains the mfERG from a normal individual who was instructed to fixate down and to the left by 8.5° off center. Notice the smaller responses in the central part of the field. These are due to the fact that with eccentric fixation, the small central hexagons are now falling outside of the fovea. Eccentric fixation can be detected by the pattern of results in both the trace array (Fig. 14A) and 3D plot (Fig. 14E). Since the fovea is now stimulated by larger hexagons, the responses in the region of fixation will be abnormally large. In the 3D plot, the blind spot has been shifted (Fig. 14B). [The latencies

of the mfERG responses can also be used to identify the foveal and blindspot regions. See ¹² and Fig. 13 in ref ⁷.] The mfERGs from patient 9 provides a clinical illustration of eccentric fixation. Patient 9 is a 64 year old woman with psoriatic arthritis who had been treated with both plaquenil and remicaid. She complained of a loss of vision OD and her visual field demonstrated a marked generalized depression (Fig. 14B). Her mfERG showed a decrease in response amplitude in the central 5° or so. However, her field depression extended at least to 25° (Fig. 14B). Before we can conclude that the retina is the site of the damage, eccentric fixation must be ruled out. The patient's visual acuity was 20/400 OD and she could not see the fixation target. Her fixation was monitored during the test and it was steady. However, her mfERG (Fig. 14D, F) indicates that she was clearly fixating off center. Notice how the pattern of her mfERG resembles that in Fig. 14C, E. The location of the foveal peak and optic disc depression are both consistent with the patient fixing up and to the left of the fixation target. Thus, her retinal function is normal and the damage must be at or beyond the ganglion cells. The message is clear. If care is not taken in the recording and interpretation of mfERGs, then depressed central responses due to fixation errors can be misinterpreted as a retinal problem.

Beware of the 3D Plot

The 3D plot can be misleading and should never be presented without the associated trace array. To illustrate the main problem with the 3D plot, consider the records in Fig. 15A. These responses were obtained from an electrode in water. There are no responses here, only noise. However, since the 3D plot (Fig. 15B) is obtained by dividing the response, which is the same everywhere, by the area of the local hexagon, which is smaller for the central hexagons, a peak is present. Figure 15C-F provides a clinical example of where the 3D plot was misleading. Patient 10, a 66 year old women with multifocal choroiditis and panuveitis, had counting fingers OD and 20/20 acuity OS. She was tested in June 2000 (Fig.15C) and then 18 months later to see if any recovery had taken place. The 3D plot in Fig. 15D suggested an improvement. However, as her trace arrays and ring averages indicate (Fig. 15E, F) there was little or no response on either day. The noisier records on the second day produced the artifactual peak in the fovea. Although 3D plots can be useful for visualizing small scotomas (e.g., Fig. 8B) and the blind spot (e.g., Fig. 14E, F), they should be used sparingly, and always in conjunction with the trace arrays.

Spatial Resolution

Since the mfERG is a topographical map of retinal function, it is important to know its spatial resolution. Spatial resolution will be influenced by a variety of factors including the degree of light scatter in the eye, the size of the hexagons in the test display, and the stability of fixation. A systemic consideration of these factors has yet to be published. In our experience scotomas at least as small as 4° can be detected (see Figs. 8 and 11 and Fig. 7 in ref. 7).

Summary

As documented above, the mfERG can be of help to the neuro-ophthalmologist. It is particularly important to emphasize the value of obtaining automated visual fields and mfERGs at about the same time, within the same day if possible. Having available topographical information from two very different tests greatly enhances the neuro-ophthalmologist's ability to diagnose difficult cases. Seeing abnormal mfERGs in the same region of the field that were abnormal on automatic perimetry provides a high degree of reassurance of the retinal origin of the defect.

Our classification of uses of the mfERG is in a sense misleading. In the overwhelming majority of the cases we have seen, the mfERG has been used to rule out the retina as the site of the disease action. In the nearly all the cases presented above, the question came down to whether there was damage to the retina before the ganglion cell. The exceptions include the cases in which the mfERG is used either to follow progression (e.g., P5) or to help distinguish among retinal diseases and/or sites of disease action (e.g., P4 and P5). These represented a relatively small proportion of the cases we have seen. The retina expert is more likely than the neuro-ophthalmologist to use the mfERG to distinguish among retinal diseases.

Recording mfERGs is not for everyone. If you already are recording high quality full-field ERGs, then recording high quality mfERGs is not difficult. Further, with experience one can learn to interpret the findings. However, the recording and the analysis of the mfERGs have all the difficulties involved in full-field ERG testing and more. Consequently, if you are not already recording high quality ERGs, then mfERG testing is best left to centers, typically teaching hospitals, with a skilled electrophysiologist familiar with the mfERG test.

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Figures

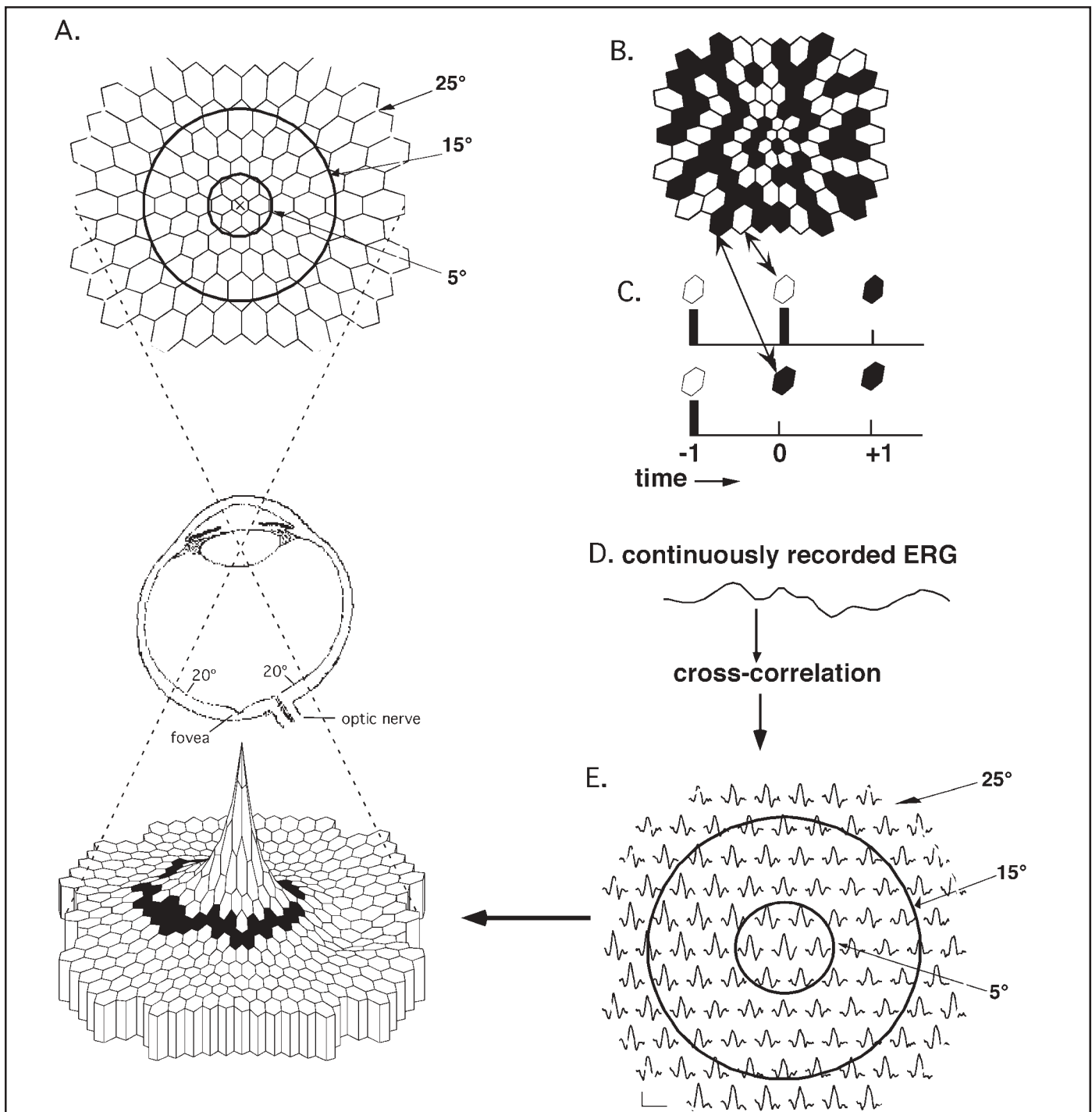


Figure 1

- A. Top: The mfERG display with circles drawn to indicate radii of 5° (red), 15° (blue) and 25° (green). Middle: A schematic of the eye to illustrate where the image of the display falls. Bottom: The 3D mfERG density plot of the responses (E) from a normal subject's right eye.
- B. The mfERG display at one moment in time.
- C. The stimulation sequence of 2 sectors in panel B.
- D. The single continuous ERG record generated by the display.
- E. The 103 mfERG responses (first-order kernel) extracted by correlating the stimulus sequence (C) with the continuous ERG record (D).

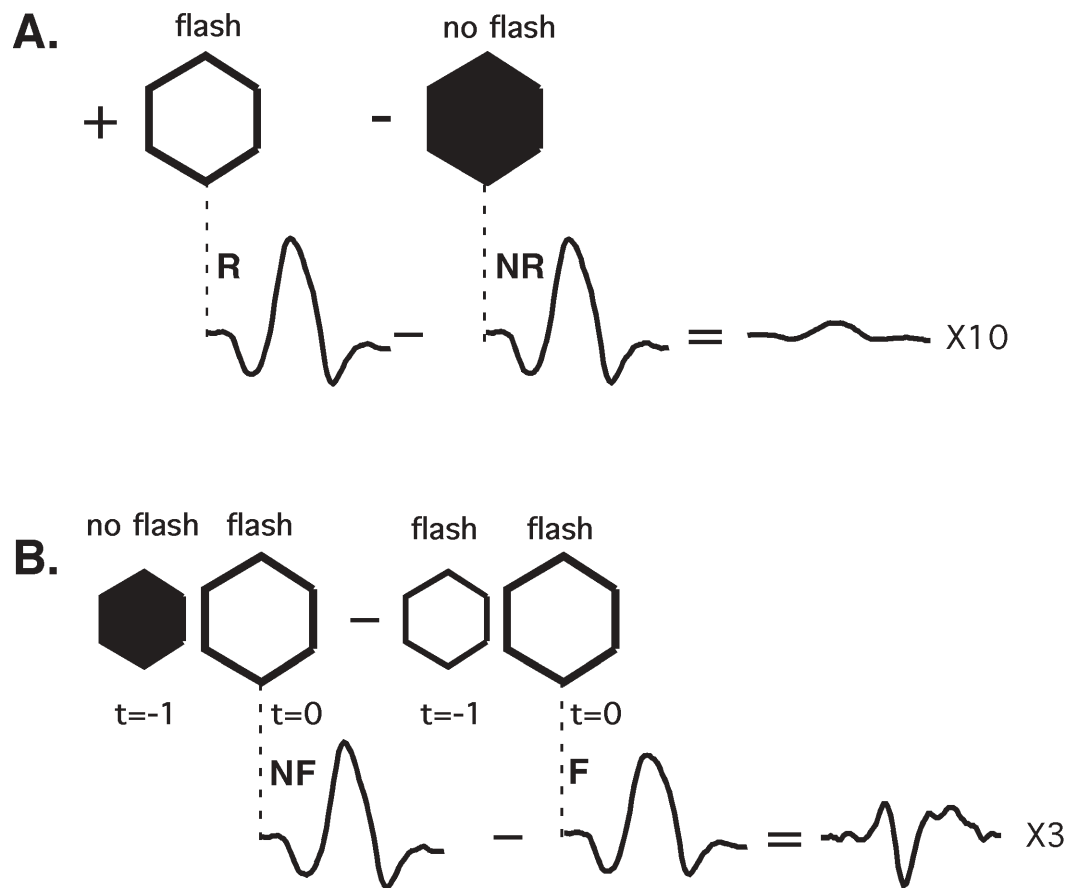
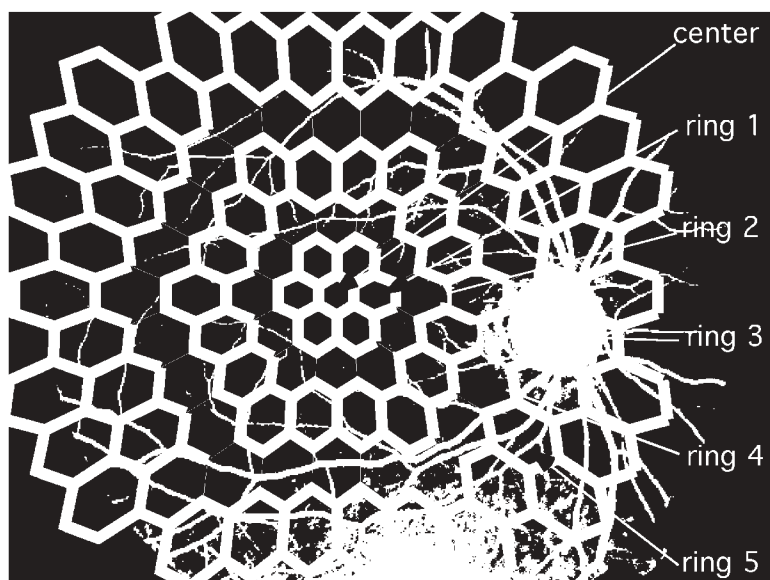


Figure 2

Schematics illustrating the derivation of the first-order (A) and second-order (B) kernels. See text for details.

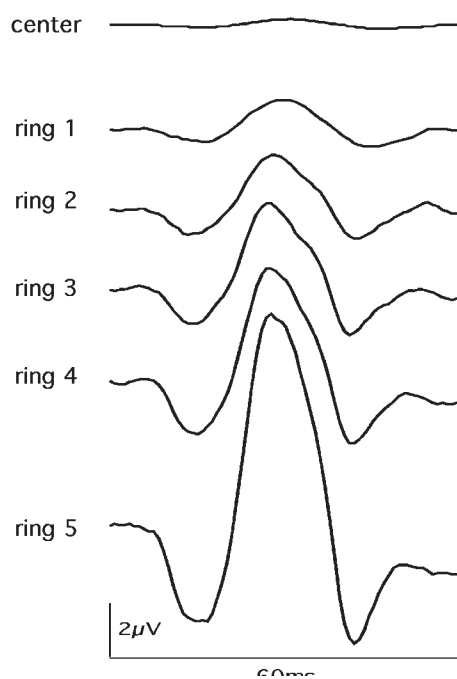
Figure 3

A.



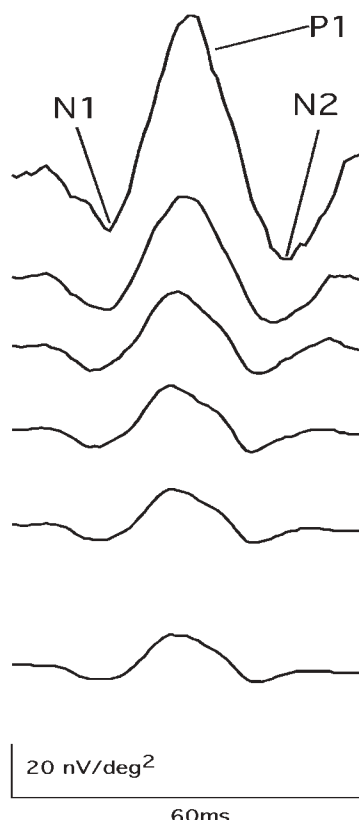
B.

Summed



C.

Response Density



- A. The mfERG stimulus overlaid on a fundus photograph. The sectors are grouped by rings about the center and marked by arrows.
- B. The mfERG responses summed for each of the rings marked in panel A.
- C. The same responses as in panel B but expressed in units of response density (nV/deg^2). That is, the summed responses in panel B are divided by the total area of stimulation in the associated rings. The principal mfERG components N1, P1 and N2 are labeled for one of the responses.

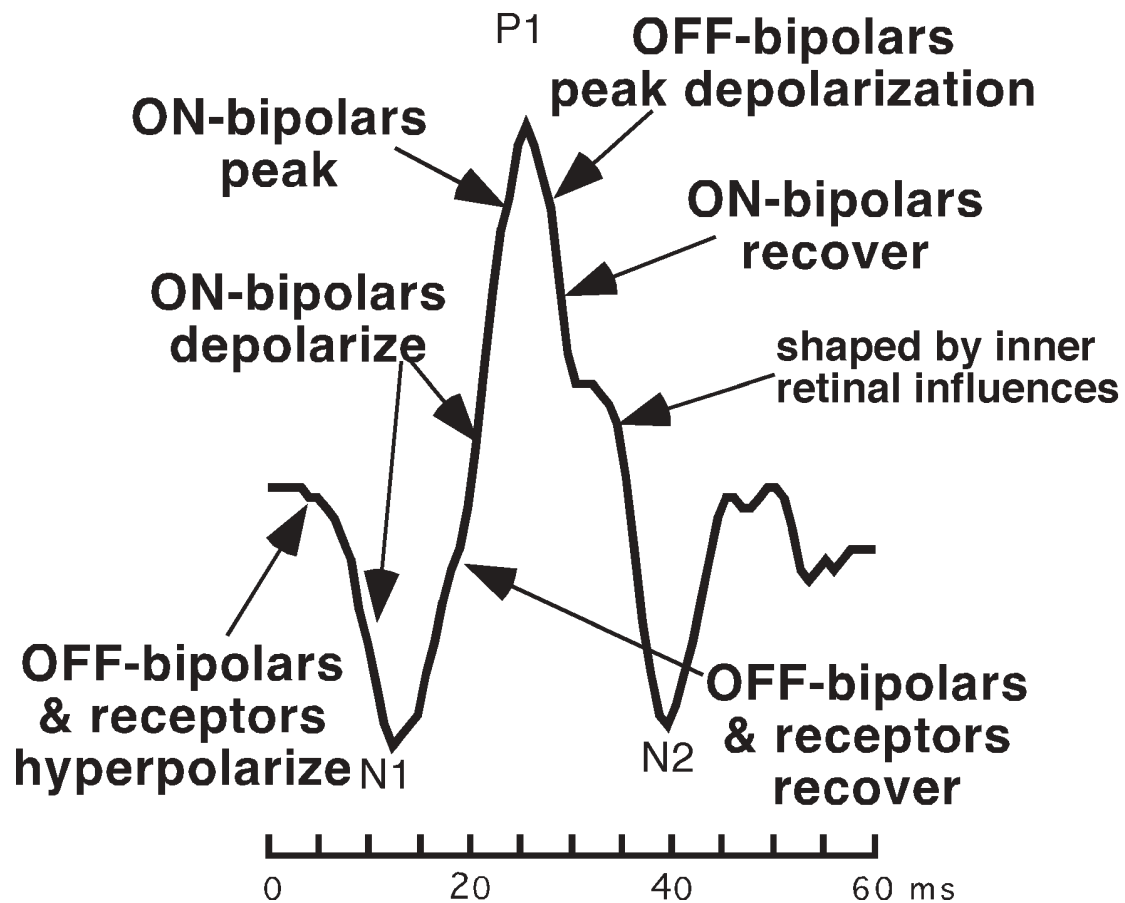


Figure 4

A model of how the different retinal cell types contribute to produce the mfERG waveform (modified from ref. 18).

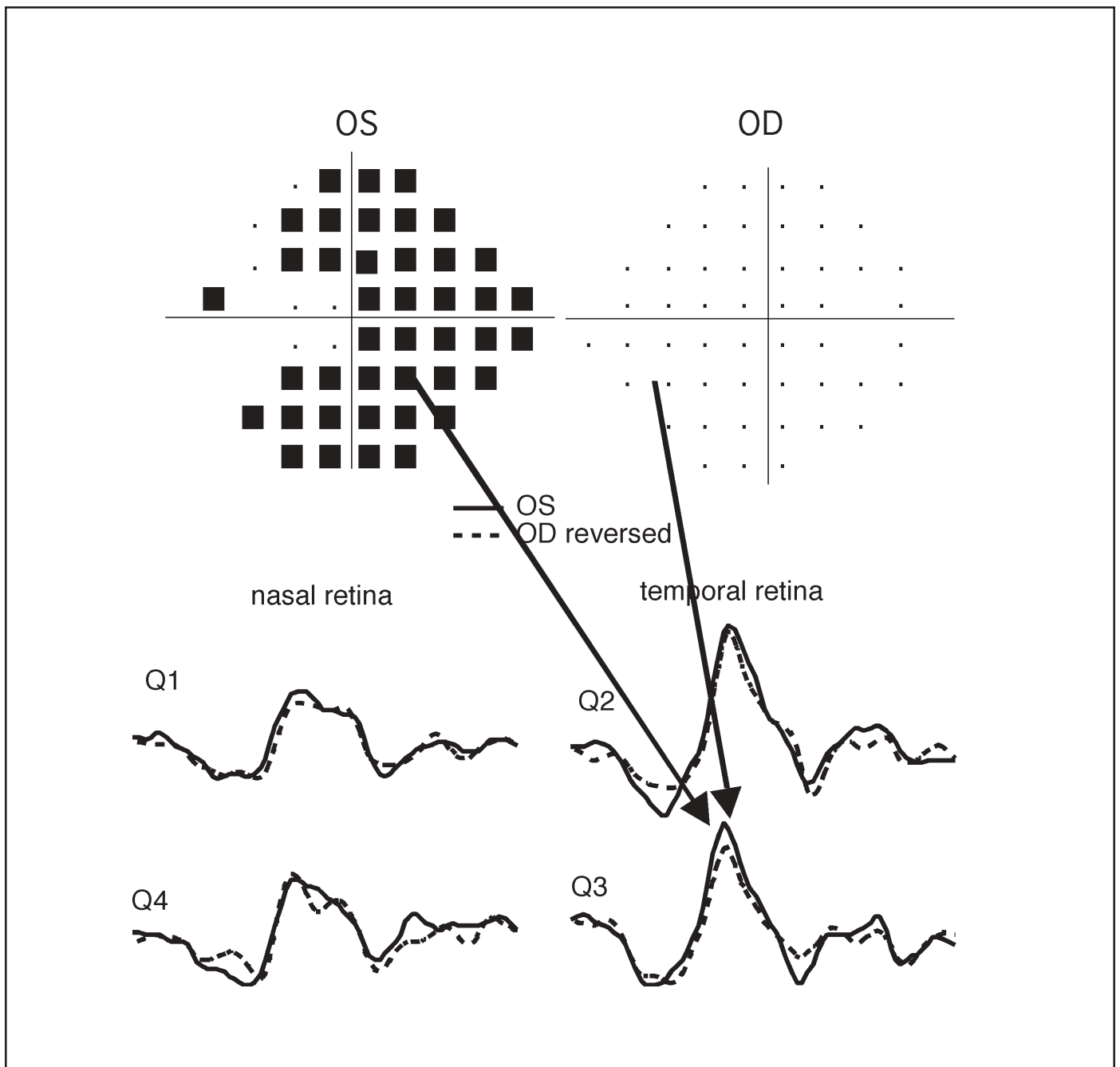


Figure 5

Top: The 24-2 Humphrey visual fields (total deviation probability plots) of a patient with ischemic optic neuropathy OS.

Bottom: The OS (red) and OD (blue) mfERG responses summed by quadrants.

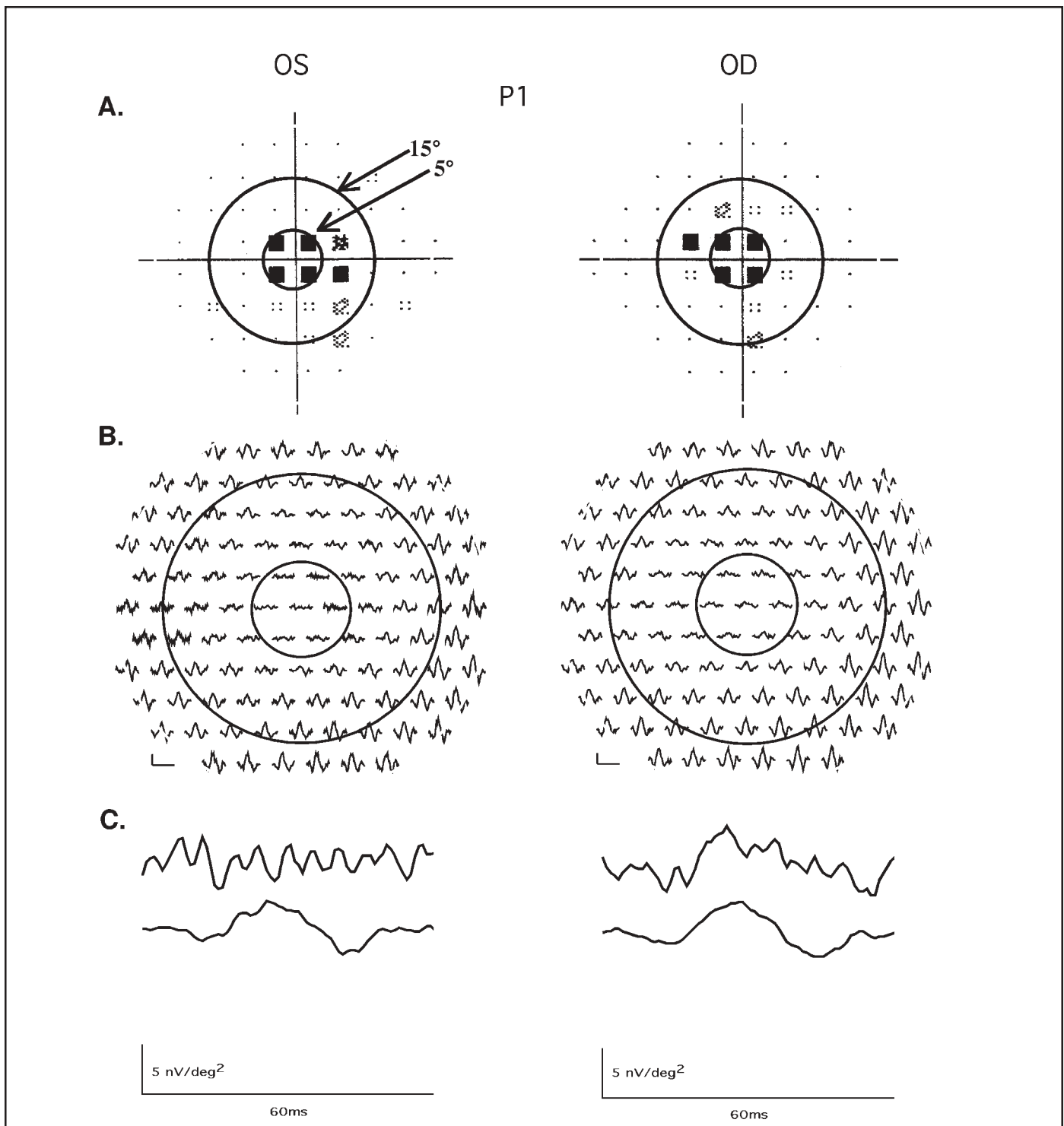


Figure 6

- A. The 24-2 Humphrey visual fields (total deviation probability plots) for patient 1.
- B. The OS (red) and OD (blue) mfERG responses for patient 1. The vertical and horizontal calibration bars indicate 100nV and 60 ms, respectively. Red, blue and green circles indicate radii of 5°, 15° and 25°, respectively.
- C. The OS (left panel) and OD (right panel) mfERG responses, expressed as response density, for the area within 5° (red), between 5° and 15° (blue), and between 15° and 25° (green).

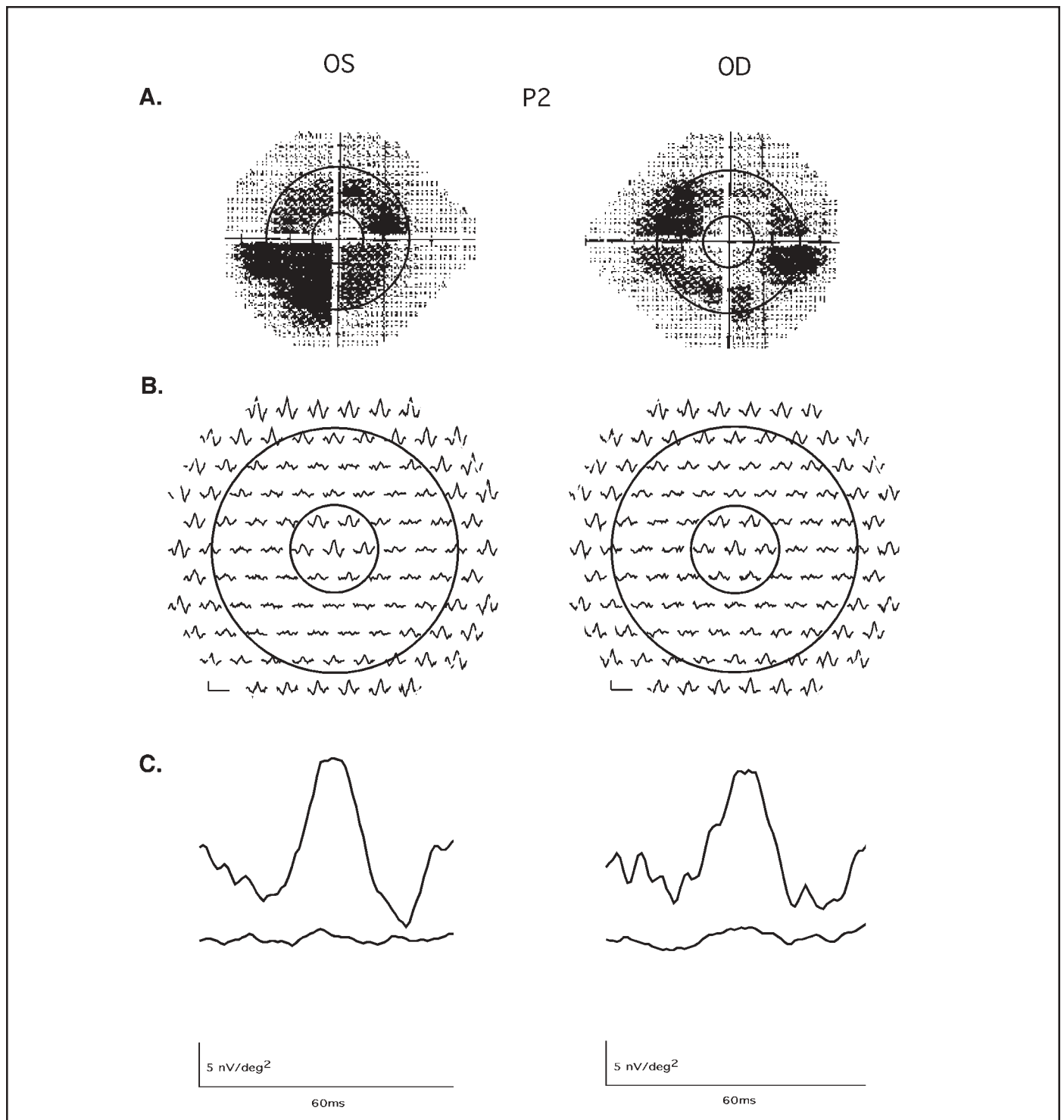


Figure 7

- A. The 24-2 Humphrey visual fields for patient 2.
- B. The OS (red) and OD (blue) mfERG responses for patient 2. The vertical and horizontal calibration bars indicate 100nV and 60 ms, respectively. Red, blue and green circles indicate radii of 5°, 15° and 25°, respectively.
- C. The OS (left panel) and OD (right panel) mfERG responses, expressed as response density, for the area within 5° (red), between 5° and 15° (blue), and between 15° and 25° (green).

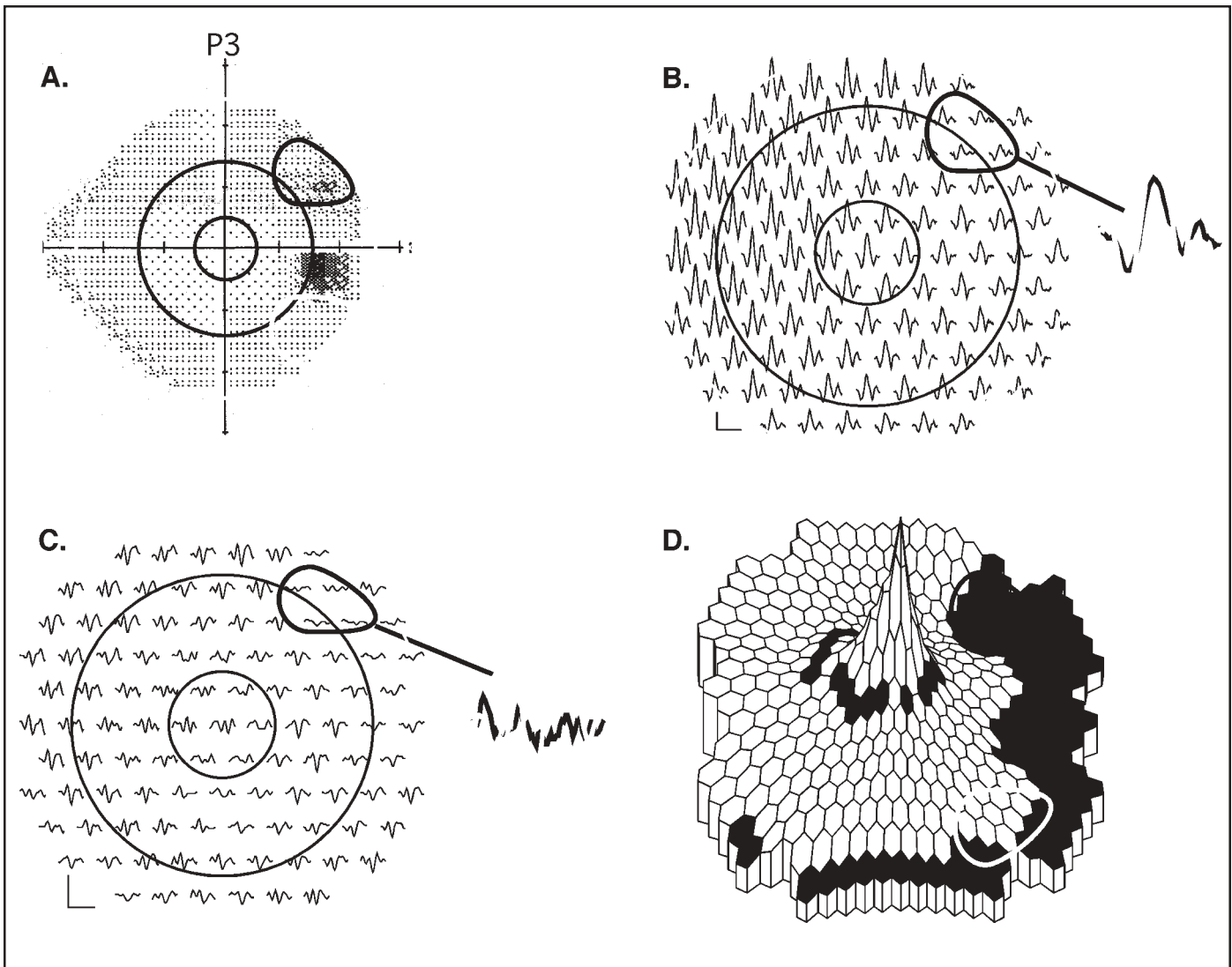


Figure 8

- A. The OS 24-2 Humphrey visual field for patient 3. A defect in the superior lateral field is circumscribed in red. A healthy, spatially equivalent area in the inferior lateral field is circumscribed in green. Geographically equivalent areas are marked in panels B, C and D.
- B. The OD mfERG responses for patient 3. The sum of the mfERG responses within the circumscribed areas are shown in the inset.
- C. The OD second-order (2K) mfERG responses for patient 3. The sums of the 2K responses within the circumscribed areas are shown in the inset.
- D. The OD first-order 3D plot for patient 3. In panels B and C, the vertical and horizontal calibration bars indicate 100nV and 60 ms, respectively. Red, blue and green circles mark radii of 5°, 15° and 25°, respectively, in panels A, B and C.

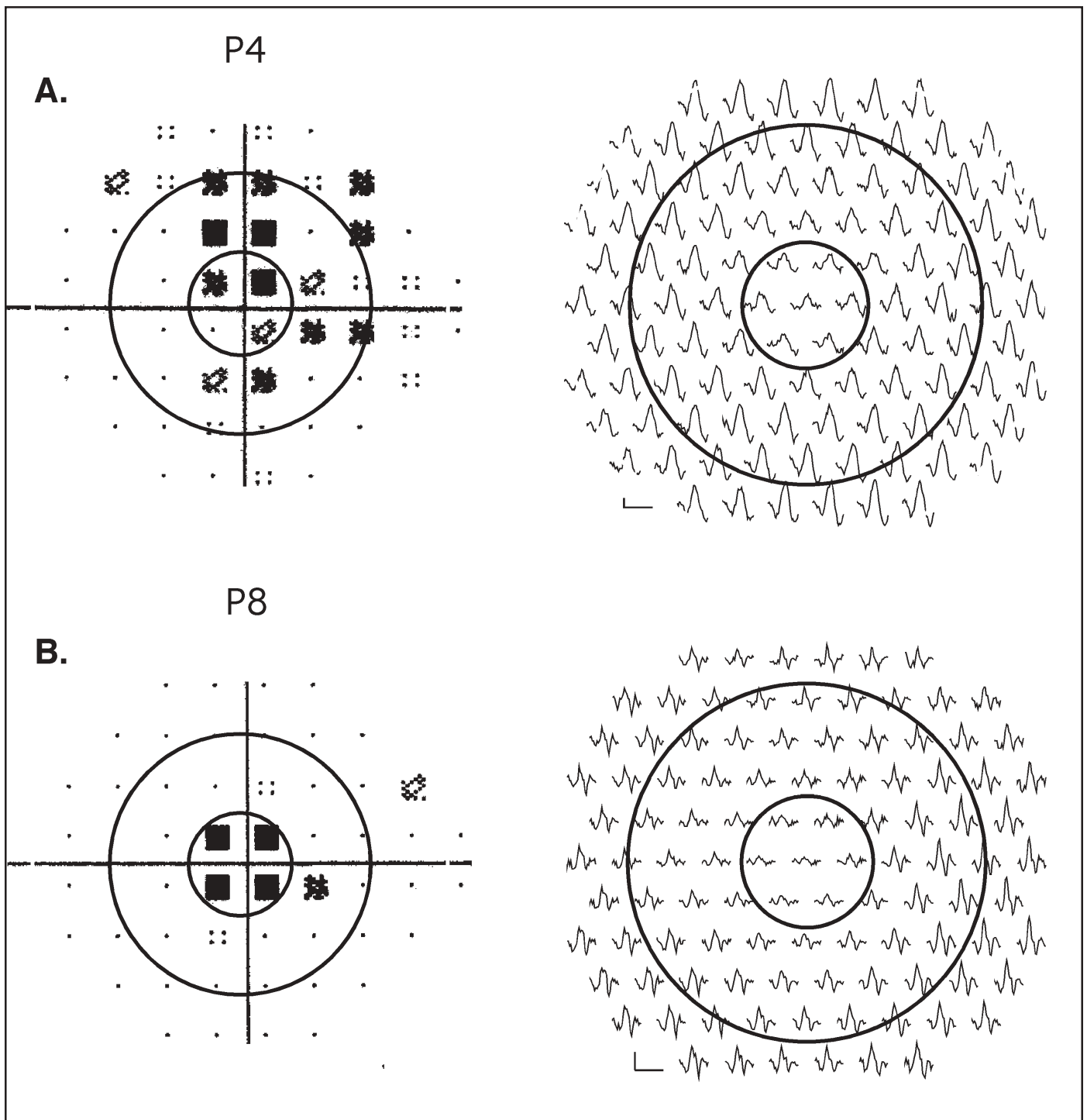
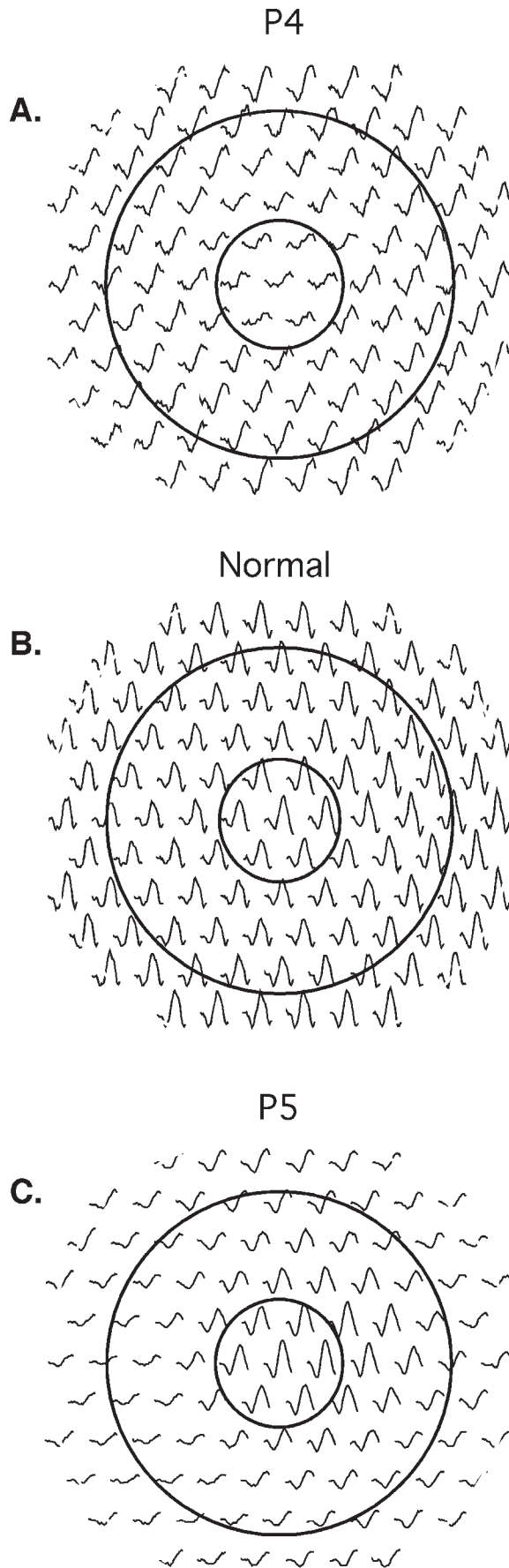


Figure 9

- A. The OS 24-2 Humphrey visual field (total deviation probability plot) and OS mfERG responses for patient 4.
- B. Same as panel A for patient 8. The vertical and horizontal calibration bars indicate 100nV and 60 ms, respectively. Red, blue and green circles indicate radii of 5°, 15° and 25°, respectively.

Figure 10

The first 40 ms of the OS mfERG responses for patient 4 (A), a normal subject (B), and patient 5 (C). Red, blue and green circles indicate radii of 5°, 15° and 25°, respectively.



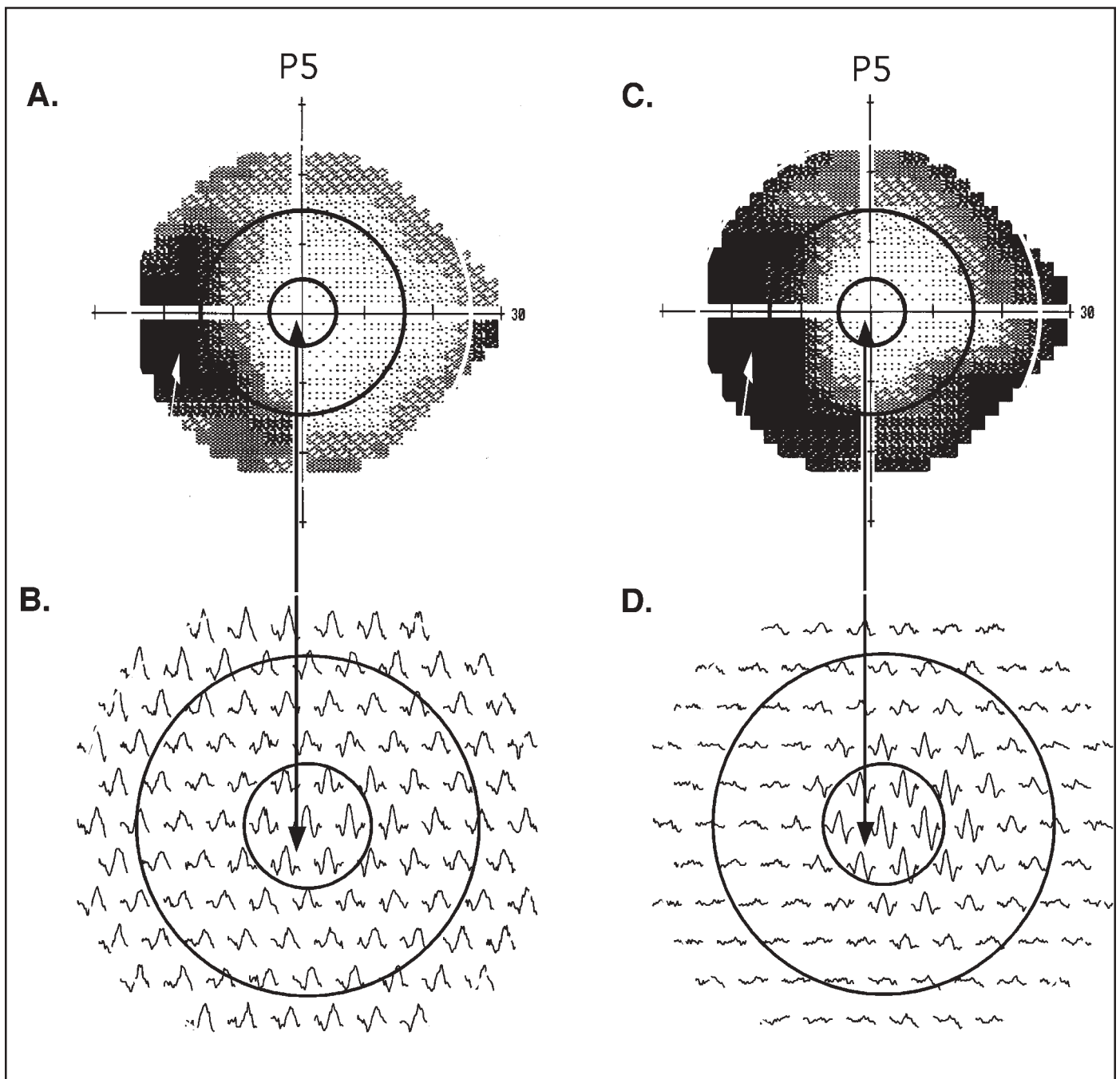


Figure 11

- A. The OS 24-2 Humphrey visual field for patient 5.
- B. The OS mfERG for patient 5.
- C, D. The 24-2 and mfERG for patient 5, 15 months later.

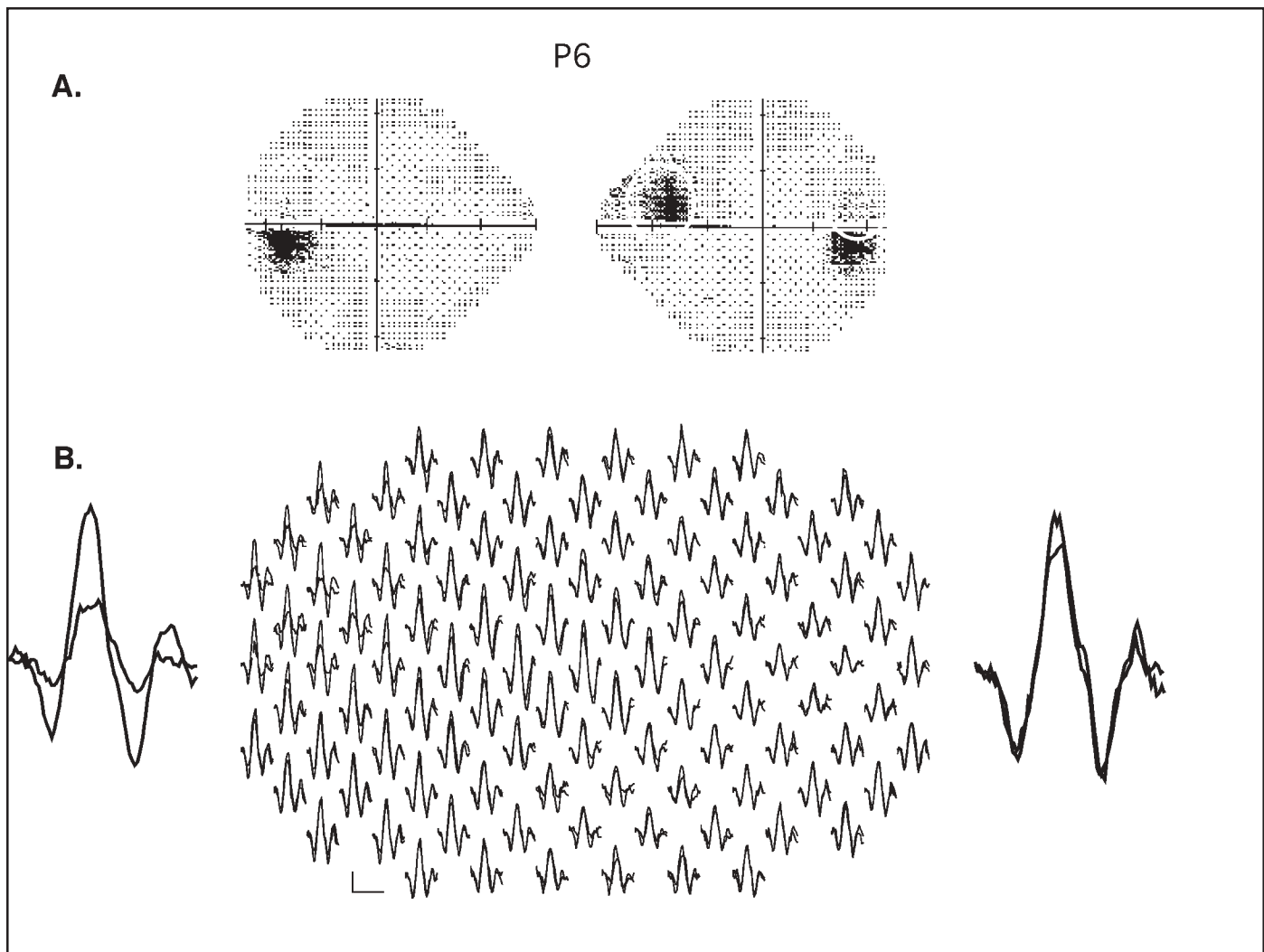


Figure 12

- A. The 24-2 Humphrey visual fields for patient 6. The green oval circumscribes a nasal scotoma OD. The magenta oval circumscribes an equivalent, but normally functioning, area in the temporal field.
- B. The OS (red) and OD (blue) mfERG responses for patient 6. The responses for the left eye are flipped about the vertical axis so that nasal field responses are presented on the left and temporal field responses on the right for both eyes. The colored ovals indicate spatially equivalent areas to those circumscribed in panel A. The sum of the responses inside the circumscribed areas are shown in the inset. The vertical and horizontal calibration bars indicate 100nV and 60 ms, respectively.

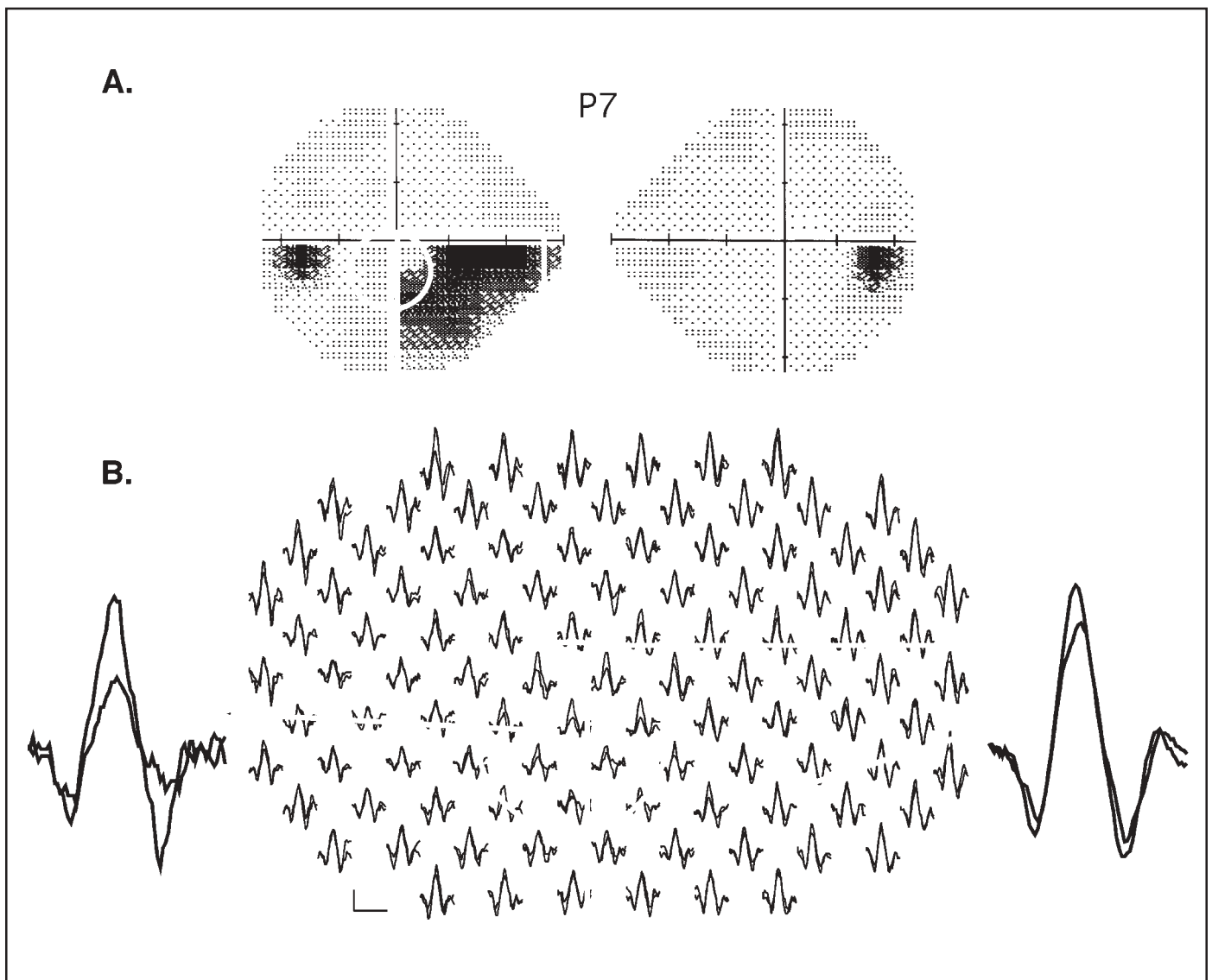


Figure 13

- A. The 24-2 Humphrey visual fields for patient 7. The green rectangle indicates an infranasal scotoma OS. The magenta circle circumscribes the paramacular region OS.
- B. The OS (red) and OD (blue) mfERG responses for patient 7. The responses for the right eye are flipped about the vertical axis so that for both eyes nasal field responses are presented on the right and temporal field responses on the left. The areas inside the green rectangle and magenta circle indicate spatially equivalent areas to those marked in A. The sum of the responses for these areas are shown in the inset. The vertical and horizontal calibration bars indicate 100nV and 60 ms, respectively.

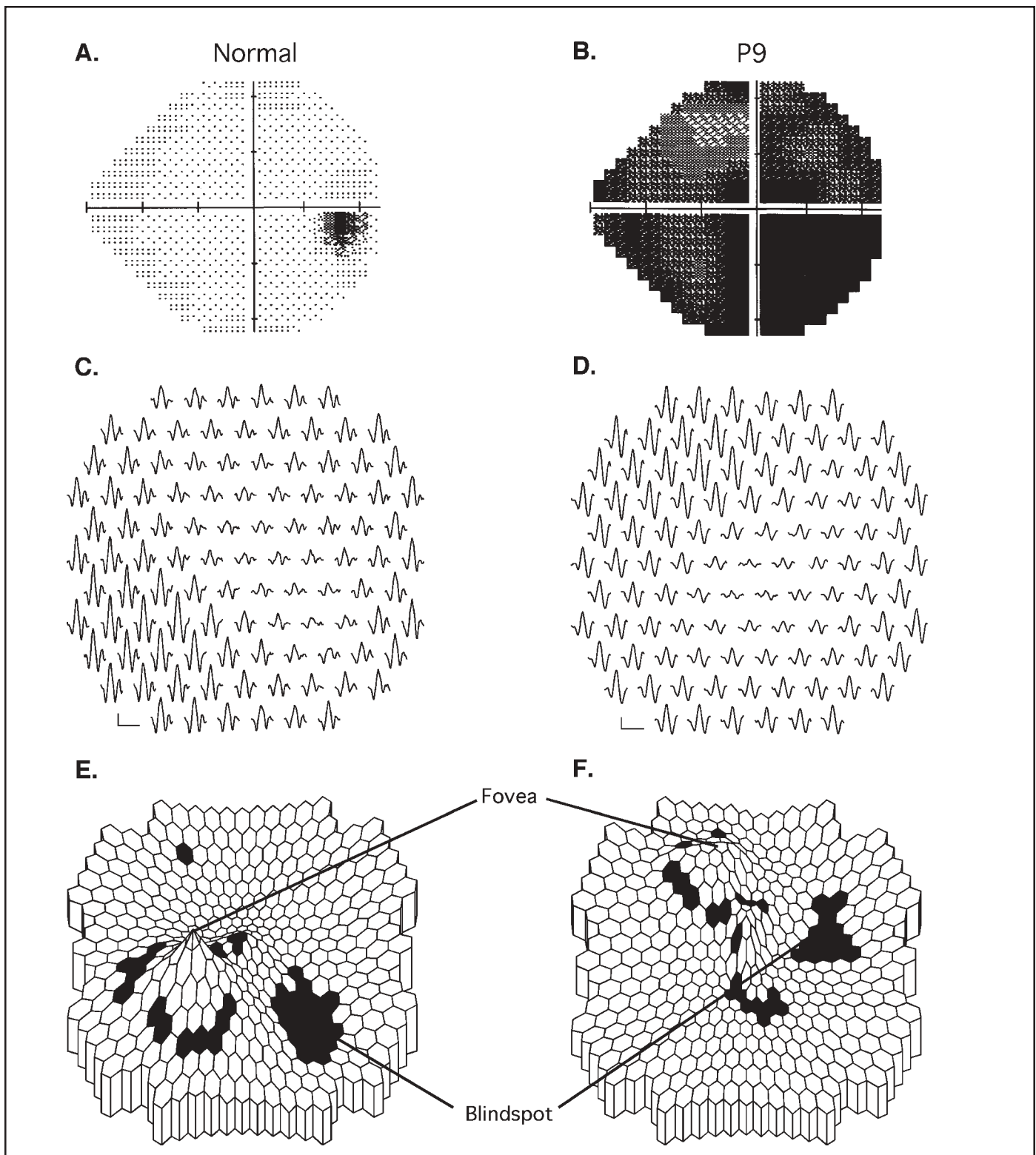
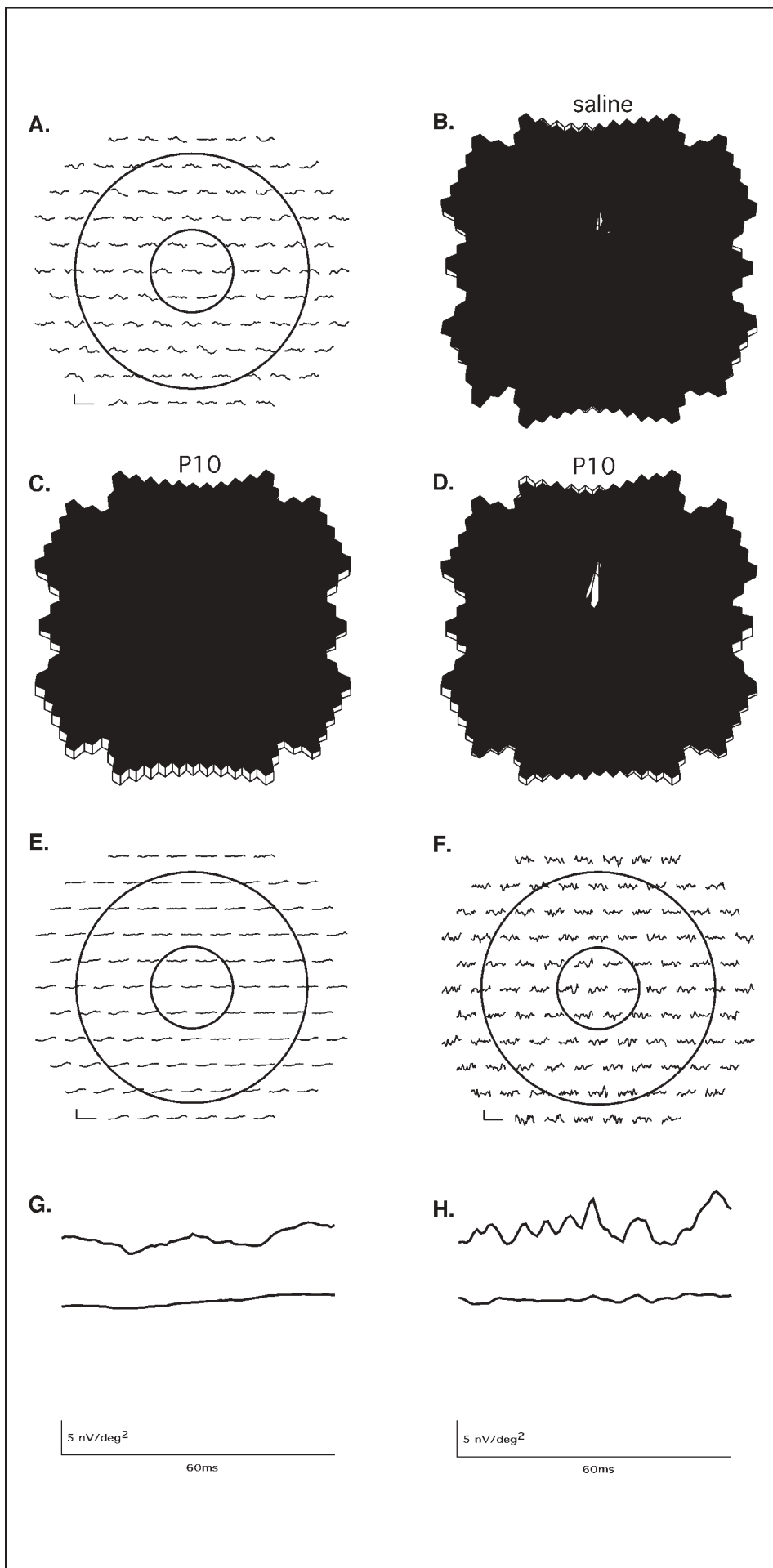


Figure 14

- A. The 24-2 Humphrey visual field for a normal subject.
- B. The OD 24-2 Humphrey visual field for patient 9.
- C. The mfERG for a normal subject instructed to fixate at a target 8.5° down and to the left of center.
- D. The mfERG for patient 9. The green circle indicates an area of apparently decreased mfERG response due to a fixation error.
- E. The 3D plot for the mfERG in C.
- F. The 3D plot for patient 9's mfERG.

Figure 15



- A. The mfERG responses for a Burian-Allen electrode placed in a jar of saline.
- B. The 3D plot for the mfERG responses in A.
- C. The mfERG 3D plot for patient 10.
- D. The mfERG 3D plot for patient 10 tested 18 months later.
- E. The mfERG responses corresponding to the 3D plot in panel C.
- F. The mfERG responses corresponding to the 3D plot in panel D. The vertical and horizontal calibration bars in panels E and F indicate 100nV and 60 ms, respectively.
- G. The mfERG responses, expressed as response density, for the area within 5° (red), between 5° and 15° (blue), and between 15° and 25° (green) of panel E.
- H. Same as panel G for responses in panel F. Red, blue and green circles indicate radii 5°, 15° and 25°, respectively.

