Multifocal ERG Reveals Several Patterns of Cone Degeneration in Retinitis Pigmentosa with Concentric Narrowing of the Visual Field

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Purpose. To analyze multifocal ERGs (mfERGs) in patients with retinitis pigmentosa (RP), with constricted visual fields and visual acuity satisfactory for steady fixation.

Methods. The mfERGs of 86 eyes of 43 patients with various forms of inheritance and durations of RP were analyzed. A retinal scanning system with a 20-in. monitor was used to map central cone function. Electrical signals of the retina were detected by using DTL fiber electrodes.

Results. The site of the best response density of the mfERGs in the patients with RP was found in a central or eccentric position of the trace array. Depending on the position of the best response density in the two eyes, the patients were categorized into three groups. In the first group, the best response density was recorded from the central hexagon in both eyes, producing a central peak surrounded by very low responses in the three-dimensional presentation. In the second group of patients, the best responses were found to correspond to the central hexagon on only one side. In the fellow eye, however, the best response density appeared to be in an eccentric position. The patients in the third group did not present a central peak in the mfERG on either side. In scattered parts of the trace arrays, several acceptable responses were observed in all three groups that might represent patches of functioning retinal cone receptors.

Conclusions. The results suggest highly variable central responses and groups of cones with preserved function in areas previously considered nonresponsive. The high variability of the central responses could be a result of variable foveal cone density, with differences in inheritance- and duration-related cone degeneration at the time of the examination. The authors stress the value of step-by-step analysis of the trace array of the mfERGs, which can reveal the still-functioning groups of cones. (*Invest Ophthalmol Vis Sci.* 2007;48:383–389) DOI: 10.1167/iovs.06-0661

Retinitis pigmentosa (RP) is a hereditary, progressive retinal photoreceptor dystrophy in which the final consequences of cone degeneration on the central vision are rather variable. Some patients maintain good visual acuity throughout life although their full-field electroretinograms (ERGs) are not measurable, and the visual field is constricted to 5° to 10°. Others, however, lose central vision, even at a young age, and are therefore much more disabled.[1] These observations are in line with the widely held notion that RP is not a homogenous disease; instead, it can reveal differing manifestations. Several morphologic,[2–4] psychophysical,[5–7] and electrophysiological[8,9] studies have been performed to reveal the course and nature of the photoreceptor loss in RP. The relationship between visual abilities and electrophysiological indicators seems to be an important practical problem in the follow-up of patients with RP.

It is well known that the full-field ERG (i.e., the gross electrical response of the retina) can be extinguished in the early stage of the disease, when the central visual acuity is still entirely preserved.[10,11] Because the traditional ERG does not seem to be sensitive enough to indicate the condition of the central retina, other methods have been sought. First, several attempts were made to use focal electroretinography for estimation of the residual function of the central retina in RP.[9,12] These techniques, however, require special procedures to minimize the effect of stray light, and in addition it is rather time-consuming to obtain responses from more than one region.

The multifocal (mf)ERG technique, which allows a high-resolution mapping of the macular area of the retina,[13] initially seemed to be a more promising method for detection of the remaining foveal cone function in some patients with RP. The first experiences obtained with this method, however, showed that there were no detectable mfERG responses in a substantial proportion of patients with RP, even if they had good visual acuity.[14–17] Most of the later investigators introduced rather strict inclusion criteria for participation in their mfERG studies. Nonetheless, mfERG alterations reflecting a progressive constriction of the visual field and generally regarded as typical of RP were found in only a proportion of the recordings. For example, only 27 (71%) of the selected 38 patients produced a recordable, "typical" mfERG in the study performed by Seeliger et al.[14] This result raises the question of the sensitivity of the method. It is rather difficult to regard an alteration as typical if it is found in only a proportion of patients with RP. Difficulty in maintaining fixation during recording is unlikely to have been the cause of the abnormal responses, because these patients were young and had good visual acuity. Alternatively, the insufficient sensitivity of the method could be responsible for its ineffectiveness in detecting residual function in this hereditary retinal degeneration. Finally, the solution of this problem could lie in the peculiar characteristics of the degenerating cone receptors. In a search for the answers to these questions, we analyzed the mfERG recordings of all our patients with RP who had sufficient visual acuity to maintain fixation. To cover the whole patient population, we analyzed the responses irrespective of whether they were of good or poor quality. Another difference relative to the earlier studies is that we repeated the stimulation monocularly in the cases in which the best responses were not in the central position (31st hexagon).

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Table 1. Clinical Data of the 43 Patients

	Patients							Eyes				
	n	Gender		Genotype		Age at Testing		Visual acuity		*n*	Visual Field	*n*
Total	43	Male	14	U	7	Mean	31.44	Mean	0.63	86	5–10°	19
				AD	10	Range	6–64	Range	1.0–0.2		10–15°	33
		Female	29	AR	12						15–20°	34
				S	14							
Group I	14	Male	2	U	4	Mean	28.64	Mean	0.86	28	5–10°	1
				AD	5	Range	14–55		1.0–0.8	20	10–15°	9
		Female	12	AR	3				0.7–0.5	8	15–20°	18
				S	2				<0.4	0		
Group II	16	Male	7	U	2	Mean	34.37	Mean	0.65	32	5–10°	2
				AD	3	Range	11–55		1.0–0.8	13	10–15°	16
		Female	9	AR	4				0.7–0.5	12	15–20°	14
				S	7				<0.4	7		
Group III	13	Male	5	U	1	Mean	31.33	Mean	0.4	26	5–10°	16
				AD	2	Range	6–33		1.0–0.8	3	10–15°	8
		Female	8	AR	5				0.7–0.5	12	15–20°	2
				S	5				<0.4	11		

n, number of patients or eyes in the corresponding group. U, Usher syndrome; AD, autosomal dominant; AR, autosomal recessive; S, simplex.

Methods

The mfERGs of 86 eyes of 43 patients with different forms of inheritance and durations of RP were analyzed. All these patients had been under the care of the same ophthalmologist in the Department of Ophthalmology for at least 3 years. Examination of the retina included both direct and indirect ophthalmoscopy and also (in individual cases) slit-lamp biomicroscopy with Goldmann contact lenses. The visual acuity of the patients was at least 0.2 in the worse eye, allowing fixation. Visual field remnants of at least 5° to 10° were detectable by Goldmann perimetry (III.4 white stimulus).

The clinical characteristics of the patients are listed in Table 1. A group of 21 age-matched individuals with good (1.0 or corrected to 1.0) visual acuity and no ophthalmoscopic or visual field alterations served as control subjects. The study was performed in full accordance with the standards laid down in the Declaration of Helsinki.

Before the mfERG was recorded, the appropriate refraction was measured and corrected for the testing distance. Pupils were dilated (tropicamide; Mydrum; Chauvin Ankepharm GmbH; Neo-Synephrine-P 10%, phenylephrine-hydrochloride, Ursapharm Arzneimittel GmbH, Saarbrucken, Germany).

A retinal scanning system (Retiscan; Roland Consult Instrument GmbH, Wiesbaden, Germany) with a 20-in. monitor was used to map the central cone function. The room light was on during stimulation. The screen–patient distance was 28 cm.

The stimulus consisted of 61 hexagons covering a visual field of 30° around the fixation site. The radius of the central hexagon was 2°. A red central-fixation cross 2 mm in diameter was used. During stimulation, each element was either black or white (93% contrast). The mean luminance was 51.8 cd/m^2, whereas the frame rate was 75 Hz.

Electrical signals of the retina were detected by using DTL fiber electrodes. For a 50,000× amplification, the filters were set between 5 and 100 Hz.

In all testing, binocular stimulation was used, but when we found the best response density in an eccentric position, we retested the patient with monocular stimulation and compared the two recordings.

The results obtained with the retinal scanning equipment were analyzed according to the ISCEV (International Society for Clinical Electrophysiology of Vision) guidelines for multifocal ERG recordings.[18] Data were analyzed with two-way ANOVA for group and for category. When ANOVA showed significant differences, post hoc analysis was performed with the Dunnett test. $P < 0.05$ was considered significant.

Results

On the basis of the best response density of the mfERGs, the patients were divided into three groups.

The patients in group I ($n = 14$) presented typical mfERGs and typical visual field constrictions on both sides. The best response density was obtained from the 31st hexagon, producing a central peak surrounded by very low responses in the three-dimensional presentation (Fig. 1). In the peripheral rings, one to two good responses were almost always obtainable (e.g., in hexagons 10, 11, or 51). The amplitudes of the scalar products in the first ring of the multifocal recordings in the patients with RP (mean: 43.06 nV/deg^2, range: 17.2–82.2) were mostly below the normal values (mean: 109.62 nV/deg^2, range: 51.3–136). The differences between these two variables are significant ($P < 0.00001$). In both the control subjects and the patients with RP, the amplitudes of the responses declined rapidly in the outward direction toward the outer rings.

In the patients with RP, the best average amplitudes were in the second and third quadrants. This finding is in concert with the generally accepted type of progressive visual field loss.

Most of the patients in this group had autosomal dominant inheritance or Usher syndrome. The severity of the alterations did not correlate well with the age of the patients. Some young patients had a low central peak of the mfERG, and there were older patients with only a mild sensitivity loss. Their mean visual acuity was 0.86, and only three patients had a visual acuity of 0.5 in the worse eye (Table 1).

In group II ($n = 16$) of the patients with RP, the best response was found in the 31st position of the trace array on only one side. In the fellow eye, the best response density appeared in an eccentric position (Fig. 2). This alteration could not be a consequence of a fixation problem, as the fusion phenomenon keeps the eyes in a motionless position during binocular stimulation. No laterality differences were found in the refraction or in the visual acuity. Further, the ophthalmoscopic picture of the macular area was similar in both eyes without any abnormality such as cystoid macular edema or epiretinal membrane. No history of strabismus or other eye diseases could be responsible for these differences. Latent exo- or esotropia was excluded by careful orthoptic examination.

In cases in which the best response density was found in an eccentric position, we repeated the stimulation monocularly, as well. In both conditions, the best responses were found

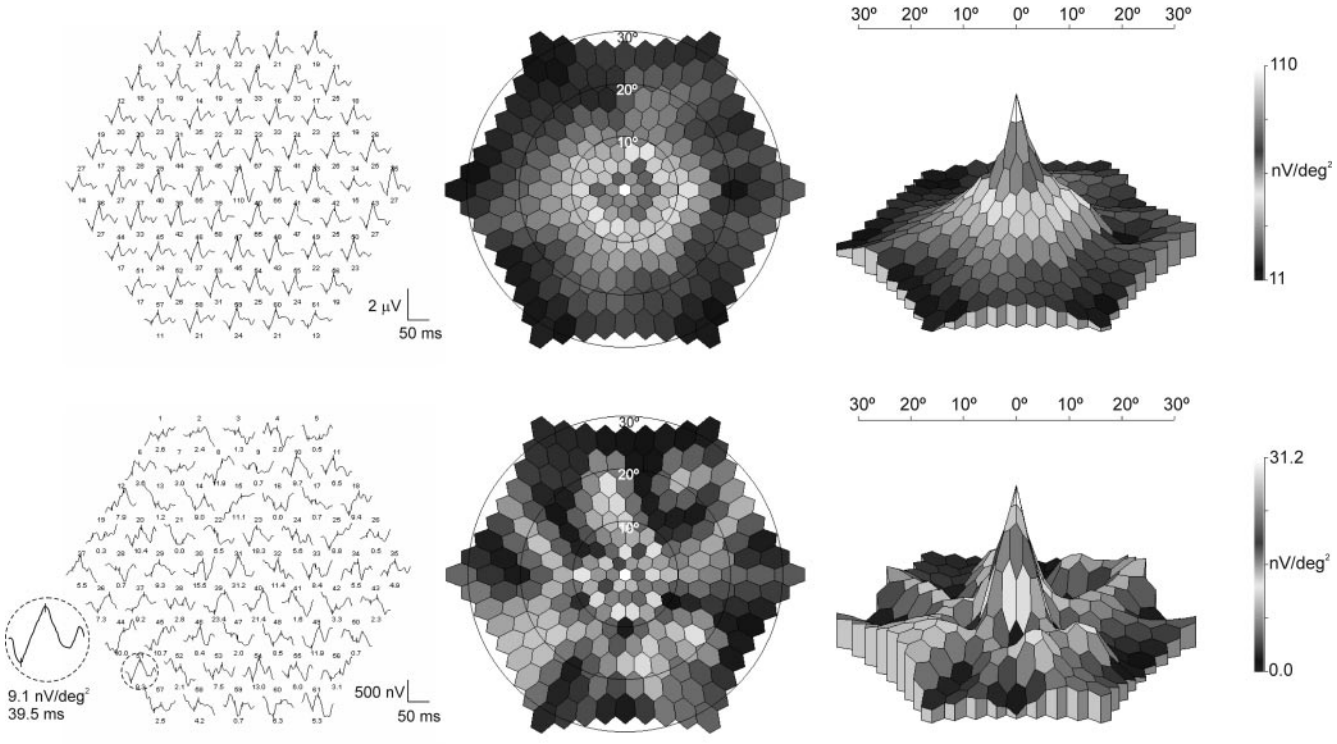

FIGURE 1. mfERG recordings of a control, healthy subject (*top*) and of a RP patient in group I (*bottom*). The best response density was in the central hexagon, producing a central peak surrounded by very low responses in the three-dimensional presentation. *Left*: trace arrays (note the differing calibration). In the *bottom left* corner, kernel 53 (*encircled*) is magnified. The density of the response and the latency of its P1 wave are indicated below it. *Middle*: two-dimensional presentations; *right*: three-dimensional presentations with calibrations.

outside the central position. In this group, the averaged mean amplitudes of the responses in the first ring of the mfERGs were lower than in group I, although some eyes had a very good central peak. Accordingly, we analyzed the mfERG findings of this group in two subgroups, depending on the site of the best responses. Group II.A comprised the mfERGs of the eyes with a central response, and group II.B those of the fellow eyes with an eccentric best position. The amplitudes of the responses in the first ring of the group II.A eyes (mean, 47.41 nV/deg^2) were almost the same as those in group I. The eyes with eccentric best responses (group II.B) produced lower amplitudes in the first ring (mean, 24.36 nV/deg^2). The results are presented in Figure 3 (second and third sets of columns). No significant side differences between the two eyes were found in the amplitudes of the third, fourth, and fifth rings or in the four quadrants.

The patients in group II had a mean visual acuity of 0.65. Altogether, 25 of the 32 eyes displayed visual acuity better than 0.5 (Table 1).

The patients in group III ($n = 13$) presented no central peak in the mfERG on either side. These cases were classified in the earlier studies as "undetectable mfERGs" or as "just noise." However, in some parts of the trace array, we found satisfactorily intact responses in all these patients (Fig. 4). In these plots, the best responses were found at rather variable sites (e.g., hexagons 17 and 47). In some cases, there were two or three peaks of low amplitude in the three-dimensional presentation of scalar products, making them "uneven," "patchy" in appearance, or "unrecordable." The mean amplitude in the first ring of the mfERGs in this group was rather low (19.28 nV/deg^2). The appearance of some characteristic, though small, responses convinced us that these mfERG recordings could not be attributed merely to artifacts or noise. Repeated examinations gave almost corresponding results. It is noteworthy that these patients also had satisfactory visual acuity (0.9–0.2, mean, 0.4). Three eyes had a visual acuity of 0.9, and 12 one had 0.5 or better (0.7–0.5).

We did not find any relationship between our groups on the basis of the mfERG recordings and the heredity pattern of the patients.

For further statistical comparison of the data, we normalized the results of ring analysis, taking the value in the 31st hexagon as 1.0 and calculating the sum of the responses in each other ring proportional to it. In this analysis, significant differences between the groups were found in only a few cases. Group I exhibited significantly smaller ring-3 values compared with those in the central hexagon in the healthy control subjects ($P < 0.05$), and the ring-1 values relating to those of the central hexagon were significantly larger in group III than in the control subjects ($P < 0.05$).

DISCUSSION

Recording of the mfERG is a relatively new electrophysiological method of mapping the functional capacity of cones in the central retinal area.[13] This is generally regarded as a useful diagnostic tool in a wide range of clinical conditions (e.g., in various forms of macular dystrophy, diabetic retinopathy, central retinal vein occlusion, autosomal dominant optic atrophy, cone dystrophy, and RP).[16]

Our results suggest that several patterns of mfERG alterations can be found in patients with RP with satisfactory visual acuity. We dealt with patients with a severely narrowed visual field and analyzed not only the typical mfERGs but also the "undetectable" mfERGs.

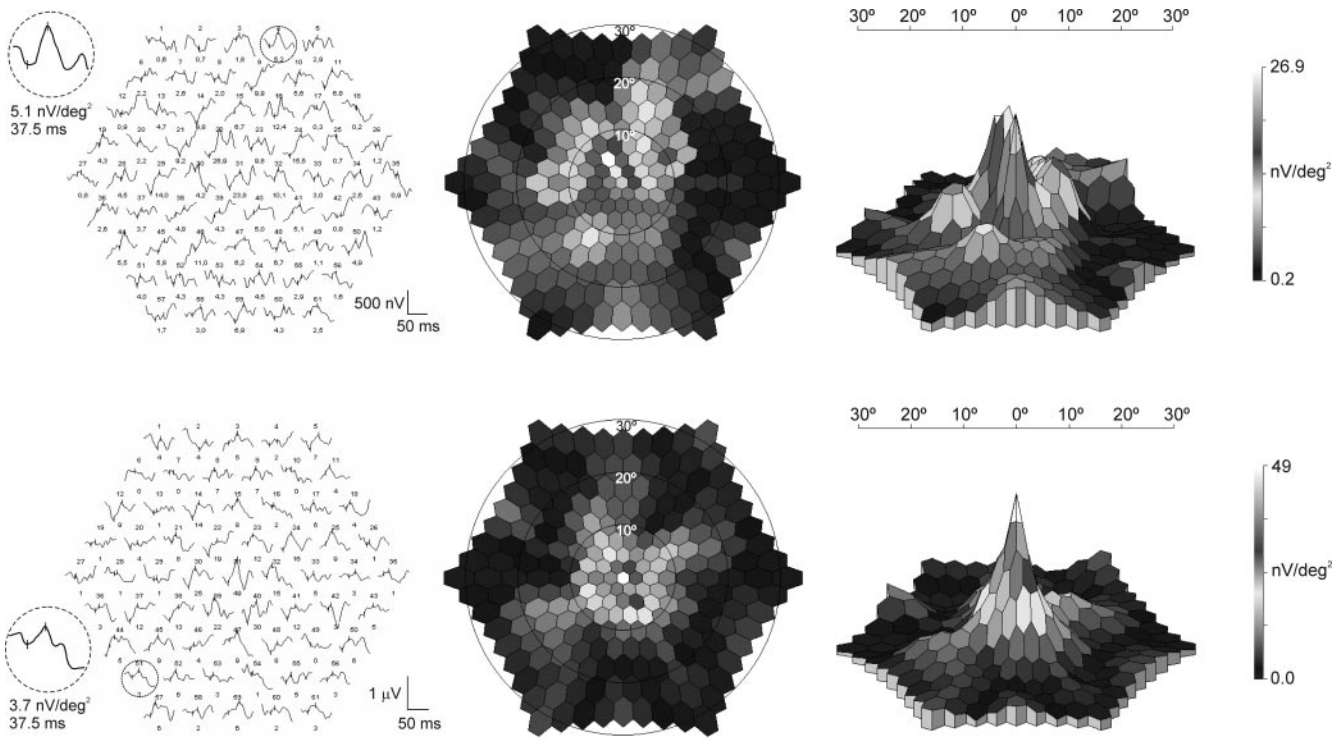

FIGURE 2. mfERG recordings of an RP patient in group II. *Top*: mfERGs of the eye with eccentric fixation; *bottom*: mfERGs of the fellow eye with central fixation. *Left*: trace arrays; *middle*: two-dimensional presentations; *right*: three-dimensional presentations with calibrations. To the *left* of each trace array, the kernel encircled is magnified. The response density of the response and the latency of its P1 wave are indicated below them.

In our normal control group, all the recordings had the best responses in the 31st position. Among the patients with concentric constriction of the visual field, we could distinguish three groups, depending on the site of the best response density in the recordings. In a large number of patients, we obtained the results found to be typical in earlier studies. Both eyes of 14 (32%) patients in group I and one eye of the 16 (37.2%) patients in group II had mfERGs with a typical central peak and diminished or extinguished peripheral responses. This number amounts to 69.7% of the eyes involved in the study, a total similar to that found in the study by Seeliger et al.[14] Among the extinguished local ERGs, we observed one to two subnormal responses with a normal wave form in the peripheral rings of the recordings in our group I. These scattered responses, which indicate a preserved function, may escape the attention of an observer who concentrates only on the typical central peak of the trace array. However, in the two-dimensional presentation of the trace array, obvious, circumscribed areas of the retina appear that indicate remnant visual functions and make the periphery of the three-dimensional presentation "uneven." These small peripheral areas could be of prognostic significance if an attempt is made to check the retinal function for replacement therapy.

In group II, the best response density appeared eccentrically in one eye, and centrally in the fellow eye. Finally, in group III, no central peak was seen, but patches of regular responses proved the existence of retinal areas with preserved cone function at parafoveal sites.

In accordance with the earlier study,[14] we did not find any relationship between our groups on the basis of the mfERG recordings and the hereditary pattern of the patients. Thus, our results suggest highly variable central responses and patches of cones with preserved function in areas previously considered nonresponsive. This could be the reason why comparisons of the normalized data and hence elimination of the "multiplication effect" revealed much lower differences between the proportions of the values of ring analysis in the patients with RP and control subjects that could have been expected on ophthalmoscopy or estimation of the visual field.

A comparison of our results and those involving a "nondetectable" mfERG in a substantial proportion of patients with RP raises several questions concerning the method used and the nature of cone degeneration in this disease.

First, we must consider the effectiveness of our method. There are two systems for recording mfERGs: the VERIS (Electro-Diagnostic Imaging, Redwood, CA) and the Retiscan (Roland Consult Instrument GmbH). In most of the earlier studies, VERIS systems were used. We used Retiscan equipment, as no substantial differences in effectiveness have been found between the two systems.[16,19] Further, there were differences in the active electrodes used. We recorded the retinal responses with DTL fiber electrodes. The signal-to-noise ratio of DTL electrodes may be worse than that of the Burian-Allen electrodes preferred in earlier studies. However, Burian-Allen electrodes could cause more stray light than the cornea alone.[16] Further, there is a prismatic effect of the contact lens, and correction of the refraction differences due to the lenses is also difficult. We additionally prefer to use DTL electrodes in our clinical routine examinations, because they are better tolerated by the patients, especially in childhood, or when the test has to be repeated.

There were differences in the stimulating conditions, too. In earlier studies, monocular stimulation of the better eye was used. We used binocular stimulation, which made it possible that the better eye could stabilize the fixation of the weaker eye.[16] Even though our patients had no history of strabismus, and there were no substantial differences in the visual acuity of their eyes, some of them (in groups II and III) exhibited the best response density in an eccentric position on one or on both sides. We therefore repeated the test by monocular stim-

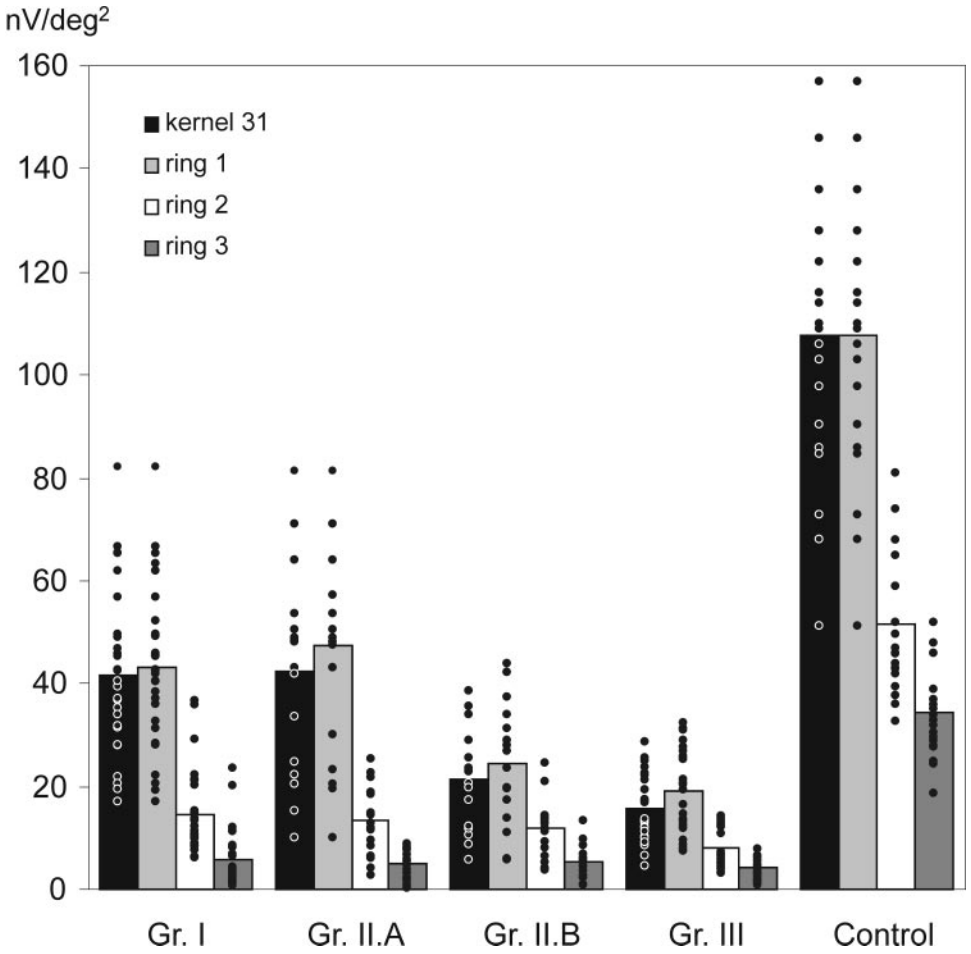

FIGURE 3. Results of ring analysis in groups I, II, and III of the patients with RP and in the control subjects. Gr. II.A denotes the values obtained from those in group II displaying central fixation, and Gr. II.B denotes those in group II displaying eccentric fixation. The ordinate indicates the mean and SE of the summed response density corresponding to hexagon 31 and in rings 1, 2, and 3. *Black dots*: individual values. (It should be noted that several dots overlap).

ulation on these eyes. We obtained almost the same results in the two conditions. In 42 (48.8%) of the 86 eyes, the best responses were not located centrally, irrespective of the stimulation technique.

The patients in group III gave very poor mfERG responses in both eyes, but all their recordings revealed two to three characteristic responses of low amplitude, in scattered sites of the trace array. Because of their typical form and their latency values, we accepted these as valid responses instead of regarding these mfERGs as nonrecordable.

After excluding the possibility that our findings could be caused by methodological differences, we have to take the problem of cone degeneration into account. There is ample evidence suggesting the involvement of cone degeneration in the foveal area of patients with RP. Among others, sophisticated psychophysical analysis has demonstrated that the contrast sensitivity function could be abnormal in early stages of RP, despite the visual acuity's being normal.[20–22] A reduced contrast sensitivity in RP has also been attributed to the damage to the cone receptors. There are several potential mechanisms for this disturbance, including the loss of photopigment or abnormalities of the membranes of the central cones.[23] However, these were ruled out by a study conducted by Seiple et al.,[5] who suggested that the functional deficits may be caused by the scattered, spatially independent loss of the receptors, with the remaining cones having normal adaptation properties.

In addition to the loss of central cone receptors, the high variability of the cone density both in the normal and in the diseased retina[2,4] could contribute to our findings. The peak foveal cone density is highly variable among individuals (100,000 to 324,000 cones/mm^2). The site at which the cone density is most variable is at the center of the fovea, where the coefficient of variation is 46%. The extent of the zone with a high density of cones could also vary in size. This striking variability in the cone density of the normal fovea may be related to variability in the rate, timing, or extent of the migration of cones during development.[24] Another factor that leads to variations in cone density is the age-related loss of photoreceptors.[25] As a third factor of variability, we may consider the disease- and inheritance-related differences of photoreceptor degeneration in RP. Because of the known relationship between visual acuity and cone density, these factors together may result in a high variability of the central responses of mfERGs.

Certainly, these deviations in cone density, including foveal cone spacing, could be limiting factors of the visual resolving power. Foveas with higher cone density may be capable of resolving higher frequencies. This could be the explanation for the high variability of visual resolving power both in the normal and in the diseased retina, in the range of 30 to 60 cyc/deg.

These facts explain why some patients can lose numerous central cones without measurable visual acuity disturbances, whereas others, with a cone degeneration of the same degree, have more severe visual loss.[7]

Overall, we assume that

1. The highly variable central responses in the mfERG could be a result of variable foveal cone density, a phenomenon present both in normal and diseased retinas.
2. The differences in disease-related cone receptor degeneration (determined by inheritance and by the different

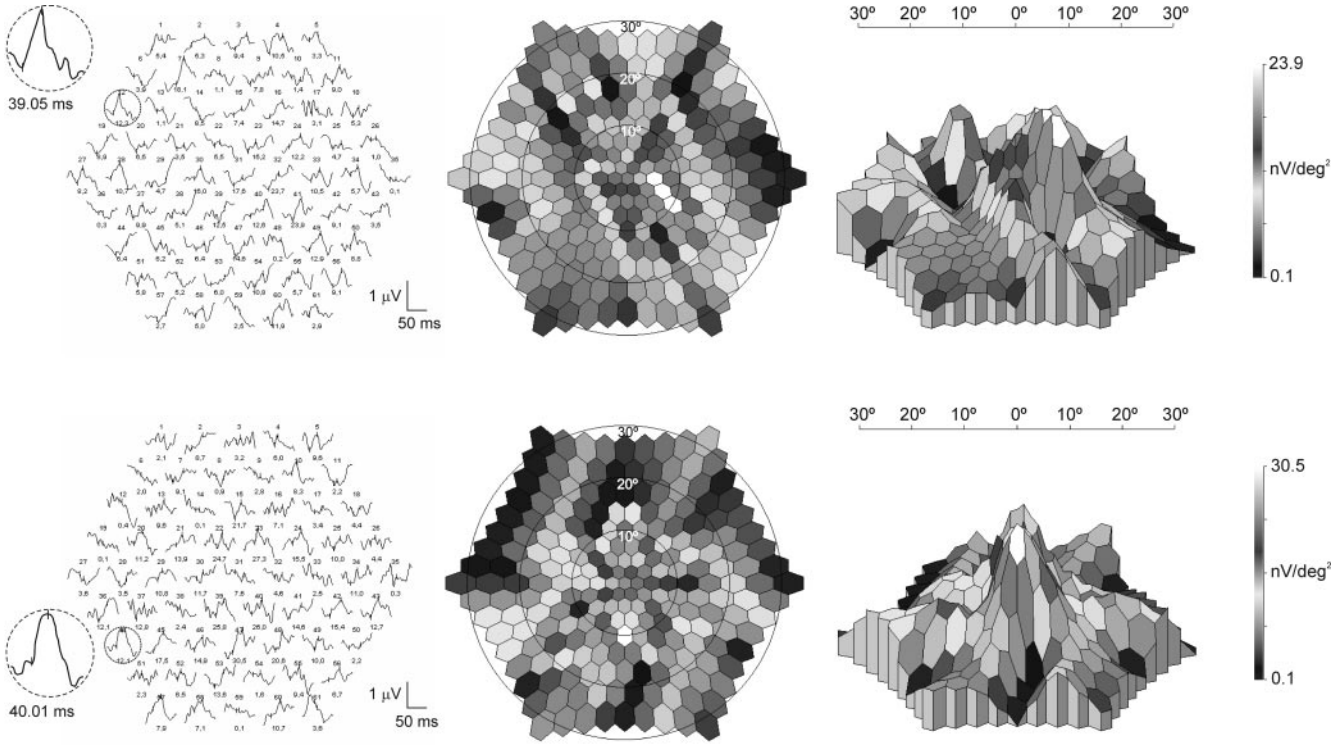

FIGURE 4. mfERG recordings of the right eye (*top*) and left eye (*bottom*) of a patient with RP in group III. *Left*: trace arrays; *middle*: two-dimensional presentations; *right*: three-dimensional presentations with calibrations. To the *left* of each trace array, the kernel encircled is magnified. The density of the response and the latency of its P1 wave are indicated below them. Values of the fourth and fifth rings are omitted. They were not informative because the amplitudes were very low.

durations of the disease) may enhance the variability of the mfERG results.

3. A scattered, spatially independent loss of photoreceptors in RP could be responsible for the patchy appearance of the remnant mfERG in the patients in our groups II and III.

As a general conclusion, we want to stress the value of step-by-step analysis of the trace array of mfERGs, which can reveal the still functioning patches of cones. The responses in these patches may not attain a level that could alter the average values in ring analysis.

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References

1. Marmor MF. Visual loss in retinitis pigmentosa. *Am J Ophthalmol*. 1980;89:692–698.
2. Stone JL, Barlow WE, Humayun MS, deJuan E, Milam AH. Morphometric analysis of macular photoreceptors and ganglion cells in retinitis pigmentosa. *Arch Ophthalmol*. 1992;110:1634–1639.
3. Santos A, Humayun MS, de Juan E, et al. Preservation of the inner retina in retinitis pigmentosa: a morphometric analysis. *Arch Ophthalmol*. 1997;115:511–515.
4. Curcio CA, Sloan KR, Kalina RE, Hendrickson AE. Human photoreceptor topography. *J Comp Neurol*. 1990;292:497–523.
5. Seiple WH, Holopigian K, Greenstein VC, Hood DC. Sites of cone system sensitivity loss in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1993;34:2638–2645.
6. Dagnelie G, Massof RW. Foveal cone involvement in retinitis pigmentosa: progression assessed through psychophysical impulse response parameters. *Invest Ophthalmol Vis Sci*. 1993;34:243–255.
7. Alexander KR, Derlacki DJ, Fishman GA. Contrast threshold for letter identification in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1992;33:1846–1852.
8. Hood DC, Holopigian K, GreensteinV, et al. Assessment of local retinal function in patients with retinitis pigmentosa using the multi-focal ERG technique. *Vision Res*. 1998;38:163–179.
9. Seiple WH, Siegel IM, Carr RE, Mayron C. Evaluating macular function using the focal ERG. *Invest Ophthalmol Vis Sci*. 1986;27:1123–1130.
10. Karpe G. Basis of clinical electroretinography. *Acta Ophthalmol Scand*. 1945;24:1–118.
11. Björk A, Karpe G. The electroretinogram in retinitis pigmentosa. *Acta Ophthalmol Scand*. 1951;29:361–371.
12. Sandberg MA, Effron MH, Berson EL. Focal cone electroretinograms in dominant retinitis pigmentosa with reduced penetrance. *Invest Ophthalmol Vis Sci*. 1978;17:1096–1101.
13. Sutter EE, Tran D. The field topography of ERG components in man. I. The photopic luminance response. *Vision Res*. 1992;32:433–446.
14. Seeliger M, Kretschmann U, Apfelstedt-Sylla E, Ruther K, Zrenner E. Multifocal electroretinography in retinitis pigmentosa. *Am J Ophthalmol*. 1998;125:214–226.
15. Kondo M, Miyake Y, Horiguchi M, Suzuki S, Tanikawa A. Recording multifocal electroretinograms with fundus monitoring. *Invest Ophthalmol Vis Sci*. 1997;38:1049–1052.
16. Kretschmann U, Bock M, Gockeln R, Zrenner E. Clinical applications of multifocal electroretinography. *Doc Ophthalmol*. 2000;100:99–113.
17. Hood DC, Birch DG. Abnormalities of the retinal cone system in retinitis pigmentosa. *Vision Res*. 1996;36:1699–1709.
18. Marmor MF, Hood DC, Keating D, Kondo M, Seeliger MW, Miyake Y. International Society for Clinical Electrophysiology of Vision:

guidelines for basic multifocal electroretinography (mfERG). *Doc Ophthalmol*. 2003;106:105–115.

19. Bock M, Andrassi M, Belitsky L, Lorenz B. A comparison of two multifocal ERG systems. *Doc Ophthalmol.* 1998–99;97:157–178.
20. Massof RW, Finkelstein D. Rod sensitivity relative to cone sensitivity in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1979;18: 263–272.
21. Young RS, Fishman GA. Sensitivity losses in a long wavelength sensitive mechanism of patients with retinitis pigmentosa. *Vision Res*. 1982;22:163–172.
22. Tyler CW, Ernst W, Lyness AL. Photopic flicker sensitivity losses in simplex and multiplex retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1984;25:1035–1042.
23. Greenstein VC, Hood DC. Test of the decreased responsiveness hypothesis in retinitis pigmentosa. *Am J Optom Physiol Opt*. 1986;63:22–27.
24. Hendrickson AE, Yuodelis C. The morphological development of the human fovea. *Ophthalmology*. 1984;91:603–612.
25. Panda-Jonas S, Jonas JB, Jakobczyk-Zmija. Retinal photoreceptor density decreases with age. *Ophthalmology.* 1995;102:1853–1859.