Principles and Practice of Clinical Electrophysiology of Vision

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The Pattern Electroretinogram

Thomas Berninger
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The pattern electroretinogram (PERG) was first recorded in 1964 when Riggs and associates[54] used the technique to record from a local retinal area. If a subject gazes at a reversing pattern such as a checkerboard, the total quantity of light entering the eye remains constant as the pattern reverses, but in the region of the retinal image, there are repetitive changes in illumination. Thus stray light cannot contribute to any response linked to the pattern reversal. It was thought that the transitions in the image from dark to light caused "on" electroretinograms (ERGs) while the reverse changes from light to dark produced "off" responses: at each reversal, the ERG actually recorded would be the sum of both these waveforms. However, it has been shown that although local changes in luminance do evoke electrical activity, part of the response is due to the presence of pattern elements. The normal response consists of at least three waves (Fig 38–1). The first, small, cornea-negative wave arises with a delay of about 35 ms and is called N_{30}; the second, a major positive wave, peaks at about 50 ms (P_{50}) and is followed by a negative trough at 95 ms (N_{95}). The use of this neutral nomenclature is recommended rather than terms such as "the pattern ERG b-wave" or "P1." Detailed accounts of physiological work will be found in earlier sections, and abnormal responses in particular conditions are described later. This chapter deals with practical clinical applications and techniques, with some background material designed to aid in appreciating the significance of clinical findings.

HOW TO EVALUATE THE PATTERN ELECTRORETINOGRAM

Amplitude

"Transient" Recording

It is generally agreed that the amplitude of the PERG is often reduced in disease while changes in the timings of the components are infrequently affected. Depending on the method of stimulation, either one or two amplitude measurements can be made. In transient conditions a positive and a negative component is found. The positive component is measured from the trough of the early deflection at around 35 ms (N_{35}) (if present) to the following positive peak around 50 ms (P_{50}). The following negative wave (N_{95}) has been measured either from the peak of P_{50} to the following trough or from the baseline to the trough. As will be shown below, the early positive and later negative portions of the waveform are differentially affected in disease and may be generated by different mechanisms. If the N_{95} is measured from P_{50} peak to the following trough, the differing contributions of the two mechanisms can be confused, for if P_{50} is reduced it will seem that N_{95} is reduced as well. Therefore it is better to measure N_{95} from the baseline to the following trough. However, the PERG is very easily contaminated by artifacts caused by eye movements, blinks, etc. While large artifacts are rejected by the electronics of the acquisition system, small ones may not be—and yet they may be larger than the PERG itself. Therefore, they may not be entirely removed by averaging. Further-

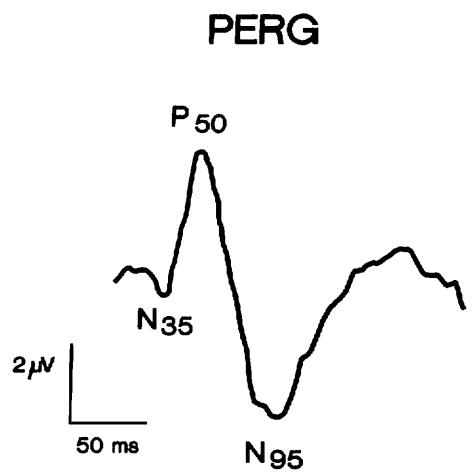

FIG 38–1.
Normal PERG with the components labeled.

more, some artifacts may be repetitive, for example, repeated corrective convergence eye movements in a patient with a degree of exophoria. For these reasons, it is common to find that a PERG has a sloping baseline, and repeating the recording may result in a similar slope. Such slopes will cause difficulties if N_{95} is measured from the preceding baseline. Two methods of improving recordings have been described.

Holder[31] described how measurements could be made in short bursts during which the patient could maintain fixation and refrain from blinking. After a few seconds, recording is interrupted, and the patient blinks, moves, and then again takes up fixation, at which point recording begins once more. Usually patients are able to cooperate well with such a schedule, and a PERG uncontaminated by baseline shift can be recorded. A second solution has been proposed by Weinstein et al.[63] They stimulated at 8 reversals per second and increased the recording time from 115 to 250 ms. With this technique they recorded a complete response (P50 and N95) and the first part of the following response (P50). Both P50s must be on the same baseline, and the baseline shift was corrected by a software program. Thus they obtained better values for the N95 component.

"Steady-state" Recording

If pattern reversals are made more frequently, a "steady-state" condition results in which the response is sinusoidal. The greatest portion of this voltage derives from the process that gives the negative component.[14] This may be measured either from peak to trough or, if a fast Fourier transform (FFT) analysis is available, the amplitude of the second harmonic response (which is pattern specific)[8, 27, 49, 50] can be obtained directly.

Latency

The latencies of the two PERG components have proved to be very stable and only rarely changed by disease. There are only a few reports about a delay of the P_{50} PERG latency. No change in P_{50} latency was found in large groups of patients with diabetes,[3] amblyopia,[6] glaucoma,[63] and macula degeneration.[2] Holder[29, 30, 32] did not see any P_{50} delay in optic nerve diseases, but he did find a significant P_{50} delay in retinal detachment, inflammatory retinopathy, branch vein occlusion, refractive error, as well as in a patient with myxoedema.[29, 32] However, Marx et al.[48] reported a significant delay of the P_{50} component in patients with ocular hypertension and glaucoma, while Howe and Mitchell[36] reported a significant delay of the N_{95} in patients with chronic glaucoma.

PRACTICAL PROBLEMS IN RECORDING RELIABLE CLINICAL RESULTS

Electrodes

To record a PERG (Fig 38–2), the optical pathway must not be degraded, and the patient must be comfortable (Table 38–1). For this reason, very lightweight, smooth electrodes made of composite materials are usually employed. The most common types are the gold foil electrode or the DTL (Dawson, Trick, and Litzkow) silver-impregnated fiber. However, other ERG electrodes have been used, including Burian-Allen lenses[34] and skin electrodes. In the former case it is essential to refract after inserting the lens: slightly larger responses can be obtained, and of course, eye movements are reduced. However, in the authors' experience, the effects of surface anesthesia on the cornea and the discomfort the speculum produces detract from long-term recordings. Again, although skin electrodes can be used, the reduction in the signal-to-noise ratio that is associated with their use is so great that they cannot be recommended.

Corneal Electrode Position

Variability in the size of the PERG can occur if the electrode position changes. The DTL thread electrode may be swept down into the lower fornix and the gold foil electrode blinked into the lateral can-

TABLE 38–1.
Hints on Useful Clinical Technique

1. The patient should be comfortable, with head supported
2. The stimulator should be 1 m or more away from the patient to reduce electrical pickup from the pattern changes
3. The area of retina stimulated should subtend more than 8 degrees of visual angle, or else responses will be very small (of course, smaller fields can be used in special circumstances)
4. The corneal electrodes should not degrade the optic pathway: most contact lenses quickly become scratched
5. Topical anesthesia may help the nervous patient but is not required
6. The electrodes should not interfere with the patient's own spectacles
7. Use the ipsilateral temple for the reference
8. The checks in the pattern should subtend 30 minutes of arc. If "nonpattern" responses are also required, use 5-degree squares
9. Surround the stimulator with a large area of brightly illuminated white card to avoid "edge effects"
10. The patterns should reverse 4–10 times/sec for transient recordings and 10–16 times/sec for steady-state recordings (see no. 18 below)
11. Sinusoidal gratings give smaller responses than checks do and can be avoided
12. Sinusoidal modulation of contrast produces a better sine wave response, but abrupt fast transitions also evoke "steady-state" records
13. If the patient blinks excessively, try "short-burst recording"[31]
14. If the baseline is unstable, the patient may be tearing: ask him to sniff: this temporarily reduces the excess tear fluid
15. If the electrodes polarize, the baseline may take up to several minutes to even partially stabilize
16. Watch to see whether averaging continues with completely flat traces; if this is the case, the amplifiers are blocking, and the equipment is not suitable.
17. Record about 200 responses and repeat 4 times. Average the values obtained in these 4 trials. The signal-to-noise reduction should be approximately 30-fold and the absolute noise level less than 0.3 μV, i.e., less than 10% of the average response, but it is unlikely to be *very* much better
18. The recording epoch should be as short as possible, consistent with the measurements to be made; 115 ms is sufficient if *only* the initial positive (P50) wave is to be estimated. If the later N95 is also to be measured, then a longer epoch of up to 250 ms is needed, so more than one complete cycle can be seen (exactly how many depends upon the repetition rate). For steady-state recordings, it may be possible to estimate the contribution of the positive and negative peaks separately by Fourier analysis[63]

thus: in both cases, the recorded response voltage decreases. Another source of variation that requires experience to detect is the averaging of eye movement artifacts: these may be 100 times as large as the PERG, and if so, most artifact rejection routines will eliminate the spurious trace. There is a greater problem with the more frequent small blinks or eye movements. These may be only five to ten times the size of the PERG and, in systems not designed for such discriminations, may be included in the averaging. Even one such eye movement record will decrease the signal-to-noise ratio to unacceptable levels. Unfortunately, such spurious voltages often resemble the PERG.

Reference Electrode Position

Another source of difficulty in interpreting clinical recordings can also be understood in terms of patterns of current flow, this time not through the retina, but through the tissues of the head. The PERG is a small response and can be easily contaminated by artifacts such as photoelectric effects and cortical potentials.[11, 64, 65] Hess and Baker[27] reported that the contamination of the PERG by cortical potentials is less than 10% when the reference electrode is positioned on the ipsilateral temple. Berninger[11] reported only a slight reduction in the positive component (P_{50}) when the reference was fixed to the ipsilateral temple or the ear, respectively. By contrast, a high, statistically significant difference was observed for the negative component. Also, in binocular recording, a statistically significant difference was only found for the negative component when the ear was used as reference point. It is possible that under these circumstances the "reference" is recording part of the cortical visual evoked response. Thus the reference electrode should be placed on the

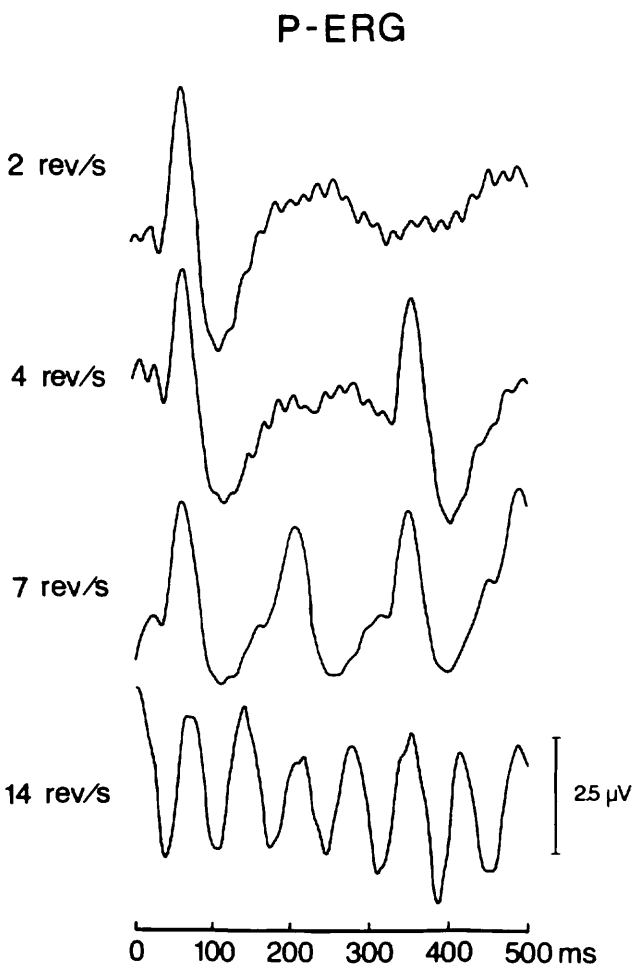

FIG 38–2.
Normal PERG recordings are shown. The first three rows are "transient" responses. The stimulus is a checkerboard pattern with squares subtending 50 minutes of arc and of 97% contrast. From the *upper row* to the *lower row* the temporal frequency increases. Note the two components, an early positive (P50) followed by a negative (N95). The actual timing varies with the equipment: mirror systems reverse at the time of command pulse, while with TV systems the momentary reversal is delayed by the raster. The *lowest row* demonstrates a "steady-state" response. The stimulus is the same as in the rows above except the reversal rate is increased to 14 reversals per second. Note that the response is approximately sinusoidal, most of the peak-to-trough amplitude due to the N95 component. (From Berninger TA, Arden GB: The pattern electroretinogram. *Eye* 1988; 2(suppl):257–283. Used by permission.)

ipsilateral temple.[11, 27, 65] This is most important when both components of the PERG are evaluated or when steady-state conditions are used since the steady-state response is a mixture of both the P50 and N95 components.

Pupil Size

The PERG has been frequently used to investigate patients with glaucoma. Since miosis is an appropriate treatment for many patients with glaucoma, the question of the influence of pupil size on the PERG is important. There is no doubt that the cortical response is affected by miosis.[26, 51] No difference was observed in the positive component of the PERG as the pupils were constricted.[11, 33, 60] By contrast, Berninger[11] observed significant reduction for the N_{95} component and a highly significant increase in latency for both the P_{50} and N_{95} components. No difference was reported for the comparison of dilated and undilated pupils.

Defocus

The PERG has been reported to be very sensitive to defocus.[1, 5, 27, 33, 44] With increasing spatial frequency an increased amplitude reduction can be observed. Hess and Baker[27] noted a 50% reduction with 0.50-D blur when 7 minutes of arc stripe size was used.

Pattern Electroretinography and Age

Intensive studies have investigated the relation between age and visual evoked potentials.[16] To our knowledge there are only three reports that described the relationship of age to PERG amplitude.[15, 43, 61] All three agree that the amplitude is significantly smaller in older subjects. Two authors[15, 43] also reported an increase in latency with age, although Trick[61] thinks that this does not occur. One possible confounding influence—age-related miosis—can be ruled out since Korth and associates[43] used a maxwellian view and Trick[61] observed an even more pronounced reduction of the PERG for low spatial frequencies. Thus the loss of retinal ganglion cells[10]—and other neurons—with age might be the reason for the age-related reduction in the PERG.

ORIGIN OF THE PERG

Clinical and Animal Research

Groneberg and Teping[24] were among the first to provide clinical evidence for the suggestion that the PERG originated from the inner retina. They examined a 55-year-old patient who had suffered an in-

jury that included a section of the optic nerve. PERGs were recorded some days after the accident and 3 months later. At the first examination the PERG and the flash ERG showed normal responses. After 3 months no PERG was recordable, and the flash ERG was unchanged. Dawson et al.[17] reported similar results. Maffei and Fiorentini[45, 46] recorded the PERG in cat before and after unilateral transection of the optic nerve. The PERG remained unaltered in the affected eye for a few days after the section, then progressively decreased in amplitude, and disappeared completely about 4 months after the section. The flash ERG remained unchanged, and both flash and pattern ERGs remained constant in the unoperated fellow eye. Maffei et al.[47] repeated the work in primate retinas and took particular care to ensure that the flash responses originated in the same retinal region as the pattern responses. Because of these observations the authors concluded that the PERG originates from structures different from those responsible for the flash ERG. They assumed that the PERG is closely related to the activity of the third-order retinal neuron, i.e., the retinal ganglion cells. Their proposal is supported by histological investigation. After a transection of the optic nerve,[35] light and electron microscopic examination of cross sections through the retina showed that pathological changes are restricted to the innermost layers. However, there are also reports that retrograde degeneration can also affect the physiology of the inner retinal layers.[18] Recently, a seemingly contrary clinical observation[25] has been reported. Thirty months after surgical transection of the optic nerve in the course of an operation for removal of an optic nerve glioma a PERG could still be recorded from the blind eye, although it was significantly reduced when small checks were used. The authors conclude that cells other than the ganglion cells produce the PERG; part of it, maybe mainly the positive component, is elicited by other retinal structures. These experiments and direct clinical observations are supported by numbers of observations on patients with partial or presumed damage to the optic nerve, for example, in glaucoma or retrobulbar neuritis.[12]

Analysis of the Pattern Electroretinogram With Penetrating Microelectrodes

The sources and sinks of the PERG have been investigated by using the technique of current source density analysis.[9, 28, 56, 57] The basis of the method is as follows: the ERG is produced by currents that flow radially through the eye (and also through part of the retina), but at some point they must enter and leave the cells of origin. When current enters a cell, the local current density must decrease. Conversely, when current leaves a cell, the local current density increases. For any small lamina in the retina (orthogonal to the electrical axis, which is essentially the same as the optic axis), current flows through the lamina down the extracellular resistance and gives rise to a voltage drop across the lamina. In experiments on the origin of the ERG, responses are recorded when the microelectrode is at the inner surface of the lamina and again after it has moved to the outer surface of the lamina. The difference in the two responses gives the voltage drop between the two positions. If the local resistance is known, the radial voltage drop gives the radial current (from Ohm's law). Now the electrode is moved on, the same set of measurements made for another lamina, and so on through the retina. Consider two laminae that are in the vitreous: obviously the current in both must be essentially the same. But in the retina, the current can change for it can enter or leave the retinal cells; thus the difference in current between successive laminae gives the sites of the sources and sinks of the ERG.

The results of various workers differ in detail, but there is broad agreement that for flashes or steps of uniform patches of light the ERG current largely originates in the outer layers of the retina, and when the stimulus is a checkerboard or grating, the sources and sinks are found in the inner retinal layers. The actual distribution of sources and sinks is complex and may be species dependent. Several different components with similar temporal characteristics may be generated in overlapping laminae. However it appears that the innermost current sink could be in the ganglion cell layer. Thus these studies directly support the results of clinical and animal research.

STIMULUS PARAMETERS AND THE PATTERN ELECTRORETINOGRAM

Spatial Frequency

One way of drawing an analogy between PERG and inner retinal activity is to examine the relationship between the size of the elements in the pattern and the response amplitude. Ganglion cells are known to respond optimally to a particular size of pattern element—to have a spatial tuning—because

the majority have concentric receptive fields in which center and surround produce opposite and antagonistic effects.[23] Although bipolar cells have center-surround organization in most animals tested, this property is most marked in the ganglion cells.

Experimental findings about the relationship between PERG amplitude and pattern size have been reported. Spekreijse et al.,[59] who made the first quantitative PERG measurements, were unable to detect any spatial tuning and demonstrated that the amplitude of the PERG was not dependent upon contrast in the same way as the visual cortical evoked responses. Some of these findings have been confirmed,[4, 52, 53] but Arden and Vaegan found that if the retina was stimulated by uniform patches of light that increased and decreased in luminance so as to mimic those that occur during the appearance and disappearance of the pattern, the resulting responses could not be summed to produce a PERG: the patterned response is always too large.[4] Under the conditions of their experiments, an optimum check size could be found that produced the largest response. However, only for small fields surrounding the fovea did they find a clear maximum. They concluded that changes in luminance produced an ERG to which the pattern response was added, and this has been confirmed by recent work. Similar results were obtained by Hess and Baker[27] and Baker and Hess,[8] who showed for smaller responses and rapid, sinusoidal changes in contrast that sharp "spatial tuning curves" could be obtained. Many other workers have reported similar results: Berninger and Schuurmans[14] evaluated the early positive and following negative component. No spatial tuning seemed to be present for the positive component for the entire range of temporal frequency, while significant spatial tuning was observed for the negative component. Korth and Rix[42] also reported that the negative component demonstrated spatial tuning that is more pronounced when the stimulus is of low contrast. It is believed that the spatial tuning for the positive component might be obscured by a luminance component.[38, 39, 49, 50, 55] The observation that only the negative component demonstrates a sharp spatial tuning helped to explain the different results in the literature. Thus most experimenters who evaluated the positive component failed to record spatial tuning,[7, 37, 62] while those authors who evaluated either the negative component[14] or a steady-state response (either by using Fourier analysis or by measuring the whole amplitude) recorded spatial tuning.[49, 50, 58, 62] At higher temporal frequency, however, the PERG is dominated by the negative component.[14]

Luminance and Contrast Component of the Pattern Electroretinogram

The most extensive investigation has been done by Drasdo et al.[19–22] and Thompson and Drasdo,[60] who have calculated the retinal distribution of illumination caused by each pattern employed and have investigated the amplitude/spatial frequency relationship for a small disk which includes the fovea and for a series of concentric annuli. It is assumed that the largest pattern elements (each one of which completely covers the area investigated) must produce an ERG caused solely by luminance changes (the retinal illumination response [RIR]). When the pattern size is smaller, there will be additional contrasting borders on the retina. When the pattern changes, an additional pattern-specific response (PSR) may also be evoked. But, at each border, the bright square scatters light into the dark. This will have two effects: the dark squares will be made brighter, so the change in retinal luminance is not so great for small as for larger squares—this will reduce the RIR. Also the PSR will be reduced because effective contrast is reduced. It is also possible to make a direct calculation of these changes from the known optical properties of the eye. If an experimental relationship between PERG amplitude, square size, nominal contrast, and nominal luminance is established, it is possible to correct for the imperfect optics of the eye and to subtract the purely "luminance" (RIR) component from any experimentally obtained PERG. The resulting PSR amplitude can also be corrected for the reduced contrast. When this is done, it can be seen that the pattern response amplitude depends upon three factors: spatial frequency, the region of the retina from which the response derives, and also which component of the PERG is considered. The maximum amplitude is achieved at increasingly high spatial frequency as the region investigated moves toward the fovea. The luminance response is larger in relation to the pattern response when the average luminance is high. The relationship between stimulus eccentricity and response varies systematically for luminance and pattern response and also for the positive and negative components (Fig 38–3).

There is a surprisingly good relationship between the relative volume of the different anatomically defined retinal layers and the amplitude of the components of the PERG tentatively ascribed to these lay-

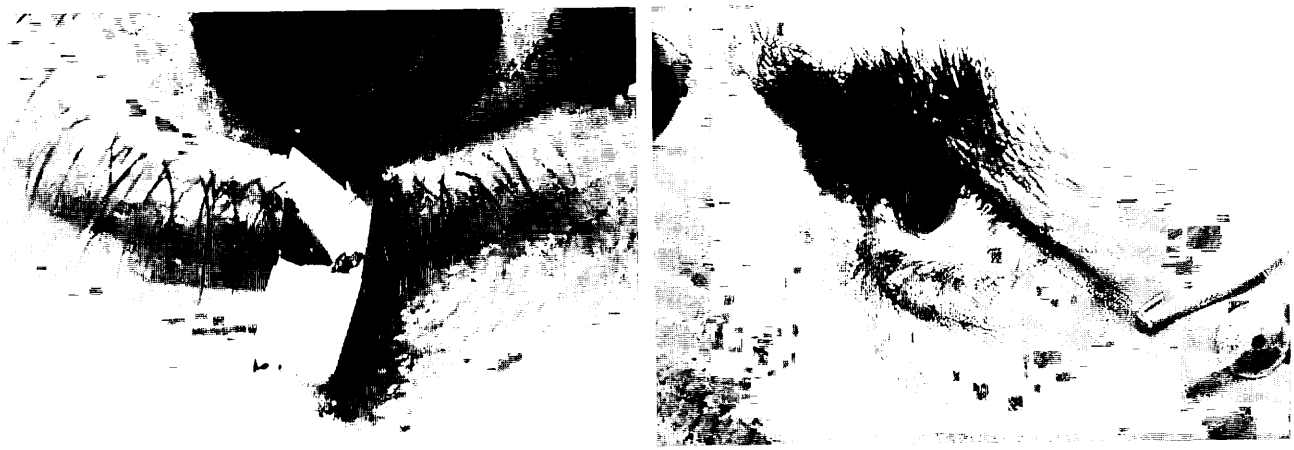

FIG 38–3.
Two common types of PERG electrodes: the gold foil (*left*) and DTL (*right*).

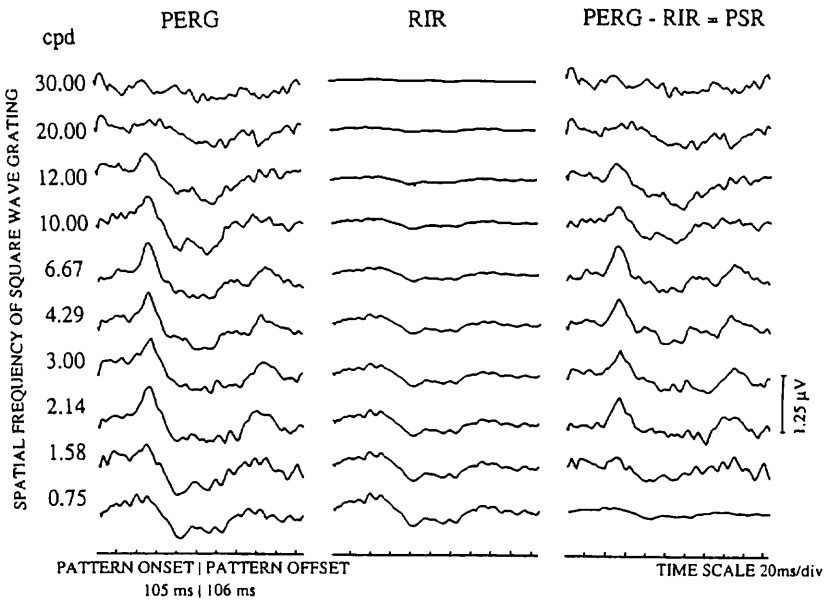

FIG 38–4.
Demonstration of two fractions of the pattern ERG. The left hand column shows responses to a grating, which has the spatial frequencies shown. The pattern appears for 105 msec every 210. Note the changes in waveform. The 0.75 c/degree grating produces a response which is related to the temporal change in the retinal illumination. Because the intensity of light scattered into dark bars by the bright light varies with the spatial frequency of the grating, the temporal contrast changes for higher spatial frequency gratings are smaller than for coarse ones, and can be calculated if the luminance/amplitude relationship for the 0.75 degree grating is known. The centre column shows the results of these calculations, the Retinal Illumination Response, RIR. The difference between left and centre columns gives the pattern specific component. Note the obvious "spatial tuning." (From Drasdon, Thompson DA, Arden GB: A comparison of pattern ERG amplitudes and nuclear layer thickness in different zones of the retina. *Clin Vis Sci* 1990; 5:415–420. Used by permission.)

ers. Thus, the luminance responses are judged to come from the outer layers and are of nearly equal amplitude for three annuli of equal area concentric with the fovea, which corresponds with anatomical findings. However, the inner plexiform and ganglion cell layers are thickened in the juxtafoveolar region, and here the positive and, especially, the negative components of the PERG are proportionately and absolutely larger per unit area of retina when elicited from regions nearer the foveola. The closest correlation is between the change in volume of the ganglion cell layer with eccentricity and the corresponding change in N95.

COLOR

In recent years we have learned that there are two visual pathways that are named after the lamination in the lateral geniculate nucleus (LGN): parvicellular and magnicellular pathways. The magnicellular pathway starts from the alpha ganglion cells, which respond poorly to color but are very sensitive to motion, flicker, and achromatic spatial contrast. The beta ganglion cells (parvicellular system) are color coded, have high spatial resolution, and are less sensitive to motion and achromatic spatial contrast. Thus the ideal stimuli for the magnicellular system are black and white patterns or gratings that are presented in reversal mode. By contrast, the ideal stimulus condition for the parvicellular system are color contrast gratings in which all the colors have the same luminance. When such color contrast patterns were used, only small negative responses were recorded for red/green stimuli, while for blue/yellow no responses could be seen at all.[13] However, such stimuli must be intense for color coded cells. It seems plausible that because the color coded beta ganglion cells are strictly linear, the responses to increments and decrements are nearly identical (which is not the case for luminance contrast, see above). The sum of the resulting current flows from many different retinal locations would therefore approximate zero, at least for the positive portion of the color PERG. Thus we may be able to separate the responses of alpha and beta retinal systems by noninvasive techniques.

When high-luminance, colored stimuli (22,500 trolands, nearly 100 times brighter) were used, PERGs to color could be recorded,[65] and this might be expected. However, the same authors[66] reported similar results when their stimuli were desaturated and only two times brighter as used in the results discussed above.

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