
Human pattern-evoked retinal responses are altered by optic atrophy

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Electrical signals in response to both diffuse flashes of light and phase-alternating spatial patterns were recorded from the eyes and from the occipital scalp of a subject with a traumatic unilateral (right) optic nerve section. Clinical examination disclosed a grossly normal right eye with no light perception, a Marcus Gunn pupil, and an atrophic optic disc. The left eye was normal. The electroretinogram responses on the lesioned side (OD) were normal, but there was no pattern-evoked retinal response (PERR) and no recordable visual-evoked response present. The conclusion is that the optic nerve and ganglion cells appear to be selectively responsible for the PERR potential. (INVEST OPHTHALMOL VIS SCI 22:796-803, 1982.)

Key words: retina, pattern stimuli, human, optic atrophy, ganglion cells, electroretinogram

The electroretinogram (ERG) is an action potential that occurs when a sudden change of illumination falls on the retina. The history of study of this potential, usually recorded from the human cornea, has been traced to Kuhne and Steiner in their 1880 and 1881 publications, according to Armington's¹ review of the area. Subsequently, many authors have contributed to the understanding of the cellular origins and components of the ERG. The best known analyses are by Granit and Riddell² and by Rodieck.³ Microelectrode studies by Brown⁴ demonstrated that in lower primates, the origins of several major and minor components of the ERG are distal to the ganglion-cell layers. Miller and Dowling⁵ used intra-

cellular techniques to show that in most vertebrates, the major component of the ERG (b-wave) probably arises from non-neuronal glia. The minor ERG components (fast potentials or oscillations), which in humans are found superimposed upon the b-wave, have been demonstrated to be of primarily photopic origin.^{6, 7} Wachmeister and Dowling⁸ argue that in the mudpuppy retina, the minor components originate at the level of amacrine cells, and Schmeisser and Dawson⁹ link those minor components to information transmission.

In the human retina, information bearing on the origins of these clinically important electrical potentials has been contributed by patient studies. Karpe¹⁰ reported that the ERG components are hardly affected in chronic open-angle glaucoma patients with severe visual loss secondary to optic-nerve and ganglion-cell changes. Feinsod et al.¹¹ examined a large number of patients with optic-nerve lesions and found varied ERG b-wave changes, some with heightened amplitude and some with reduced amplitude. In animal research, Granit and Helm¹² found the ERG to be unresponsive to antidromic electrical

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stimulation of the optic nerve and presumably the retinal ganglion cells.

The retina may also be stimulated by moving patterns or counterphasing gratings. Pattern movement may be temporally linked to computer averaging of signals so that very small potentials may be recorded. Some of the earliest responses of this type were reported by Armington et al.,¹³ who utilized the Riggs scleral plastic electrode. Recent ERG electrode improvements^{14, 15} have increased recording safety and comfort while providing a more useful optical pathway. When the optical pathway provides a quality retinal image, pattern-evoked retinal responses (PERRs) of favorable signal/noise ratios may be recorded from the human cornea.^{16, 17} Under optimal conditions, these signals are about the same size as the cortical visual-evoked response (VER) and may be used to estimate spatial stimulus resolution threshold. Maffei and Fiorentini¹⁸ could not elicit this signal from the cat retina after optic-nerve section, although ERG signals were reported to be normal.

This article reports the results of the simultaneous pattern stimulation of both eyes in a teen-age human male, who had suffered a traumatic section of the optic nerve in one eye 15 months earlier.

Methods

The subject, a 14-year-old white male, sustained a severe facial injury while water skiing. After stabilization of his condition at a local hospital, he was transferred to the University Hospital. His physical examination on arrival (04/14/80) revealed an obese, belligerent young man with a marked swelling on the right side of his face. His right lid was ecchymotic and swollen shut, with a 1.25 cm tissue laceration just above the right brow. The left eye was completely normal. Skull x-rays showed no airfluid levels in his sinuses, but there was a possible right posterior orbital fracture. An EMI scan revealed diffuse cerebral edema, right frontal contusion, and a questionable fracture extending into the optic canal but without convincing evidence of invading bone fragments (a slight "smudge" vertical opacity within the canal—probably a "ghost artifact").

The Ophthalmology Service was called to examine the patient at this point. Although conscious,

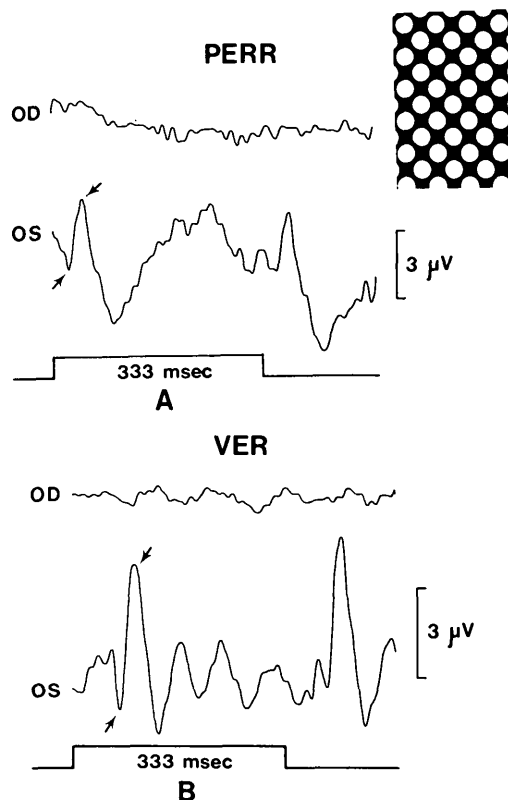


Fig. 1. Signals evoked by counterphased (1.5 Hz, 40 min arc) pattern stimuli. **A**, Recorded from the corneas simultaneously. A typical stimulus matrix is shown in the inset. **B**, Recorded sequentially, OD with OS covered and OS with OD covered. Assistance with OD position was required. A total of 165 responses were averaged. Major negative and positive signal components (arrows) were at (A) 26 and 47 msec and (B) 74 and 96 msec. Pattern movement square-wave period was 666 msec.

he would not voluntarily move his eyes and would not follow a light, but his random eye movement revealed full excursions. He would not respond verbally to a test for acuity, but he had a definite right Marcus Gunn pupil (no direct response but good consensual response). There was a question of nasal margin blurring of both discs. On 04/16/80, the periorbital swelling on the right had markedly decreased. His mental status had improved so that acuity could be determined. There was no light perception on the right, at least 20/50 on the left.

The right Marcus Gunn pupillary defect was thought to be caused by optic-nerve damage by the right orbital fracture. Still, it could have been

secondary to the orbital edema. Exploration of the right optic canal to decompress the optic nerve was considered, but past experience with this procedure has not been good. (That is, vision has not been restored after such surgery.) Hence, conservative treatment was chosen, with close monitoring of the eye. Within 3 days of admission, he was transferred from the intensive care unit. He continued to show improvement in his mental faculties. At the time of discharge (04/19/80) he had no focal deficits; his neurologic examination was normal aside from his right-eye findings (no light perception, no optic atrophy as yet, and minimal periorbital swelling).

He has been followed on several occasions since then, the last being on July 15, 1981, 15 months after the injury. At that time, vision OD had remained no light perception; OS was 20/20. Full ocular rotations were present with 15 D of right exotropia. The external and slit-lamp examinations were normal OU. The right fundus showed a marked primary optic atrophy and normal appearing retinal vessels; the left disc remained normal.

In summary, this subject sustained blunt damage to the right optic nerve, probably somewhere in the optic canal, with no damage to the globe itself. Fifteen months later he had no light perception and marked optic atrophy on the right, and the left eye was totally normal.

During the experiment, the subject partially reclined on an examining table and directly viewed a tangent screen, which subtended a 31° by 22° visual angle on which the patterned stimuli were projected. The patterned stimuli were photolithography dot matrices where 50% of the area was transparent and 50% was relatively opaque. The transparencies (Fig. 1, A) were projected on the tangent screen and formed spatial patterns of several frequencies, ranging from 5.6 to 1.2 cy/deg. These sizes correspond to individual pattern elements that subtended from 5.4 to 25 min arc. During stimulation, the light and dark areas of the projected patterns were exchanged in square wave fashion (counterphasing) at rates of 1.5, 3.5, or 8 Hz. Average luminance for the PERR stimuli was 1.65 log foot lamberts. The measured contrast was 42%. A small fixation spot was provided at the center of the screen. For the recording of responses to diffuse light stimulation of the retinas, the patient lay supine on the examining couch with the eyes directly below the center of a hemisphere that subtended approximately 120°. Diffuse illumination of the sphere provided a relatively uniform, white adapting field from a tungsten source with neutral density filters, so that the adapting retinal

illumination was approximately 1000 trolands. A second light channel provided a xenon arc flash illumination of the hemisphere. The output of the xenon source was filtered so that stimuli were delivered that were approximately 2 log units above normal threshold (20 μ V) for ERG b-wave production, with a 1000 troland adapting field. In the dark-adapted condition, the stimulus luminance was adjusted to a level approximately 2 log units above b-wave threshold (20 μ V) in normals 15 min after the offset of adaptation at 1000 trolands. The xenon flash source provided stimulation every 4 sec. For response averaging, a trigger pulse from the xenon source was led to the averaging computer and magnetic tape recorder. A similar trigger pulse was derived from the square-wave generator, which provided for counterphasing of the patterned stimuli.

Before the experiments the subject and his parents were informed about the experimental procedures and risks as required by institutional informed consent policy. No cycloplegic or mydriatic drops were used. Two drops of tropicamide HCl (Ophthaine) were applied for corneal analgesia during the application of DTL corneal recording electrodes.^{14, 17} Reference electrodes of the Ag-AgCl type were attached with electrode paste at each outer canthus. A ground electrode was attached to the forehead. VERs were recorded from an active site on the midline, 2 cm above theinion with an earlobe reference site.

Solid-state amplifiers were used with a passband from 0.2 to 1 kHz (3 dB points). Signals recorded from each eye and from the scalp electrode were led separately to input channels of a four-channel FM tape recorder for permanent storage. One channel was used for voice and for stimulus marker purposes. Signals were also led to the inputs of a multiplexed A-D converter that communicated with a general-purpose computer for on-line averaging and processing. The computer could be triggered by the phase reversal of the transparency. Recordings from the eyes were always made simultaneously, and VER recordings were made with one eye occluded. ERG recordings are the result of 20 averaged responses to diffuse xenon flashed stimuli. PERR results are the average of 160 to 1500 pattern counterphasings.

Results

The greatest amplitude signals produced in the normal OS were with patterned stimuli, larger spatial frequency, and lower temporal

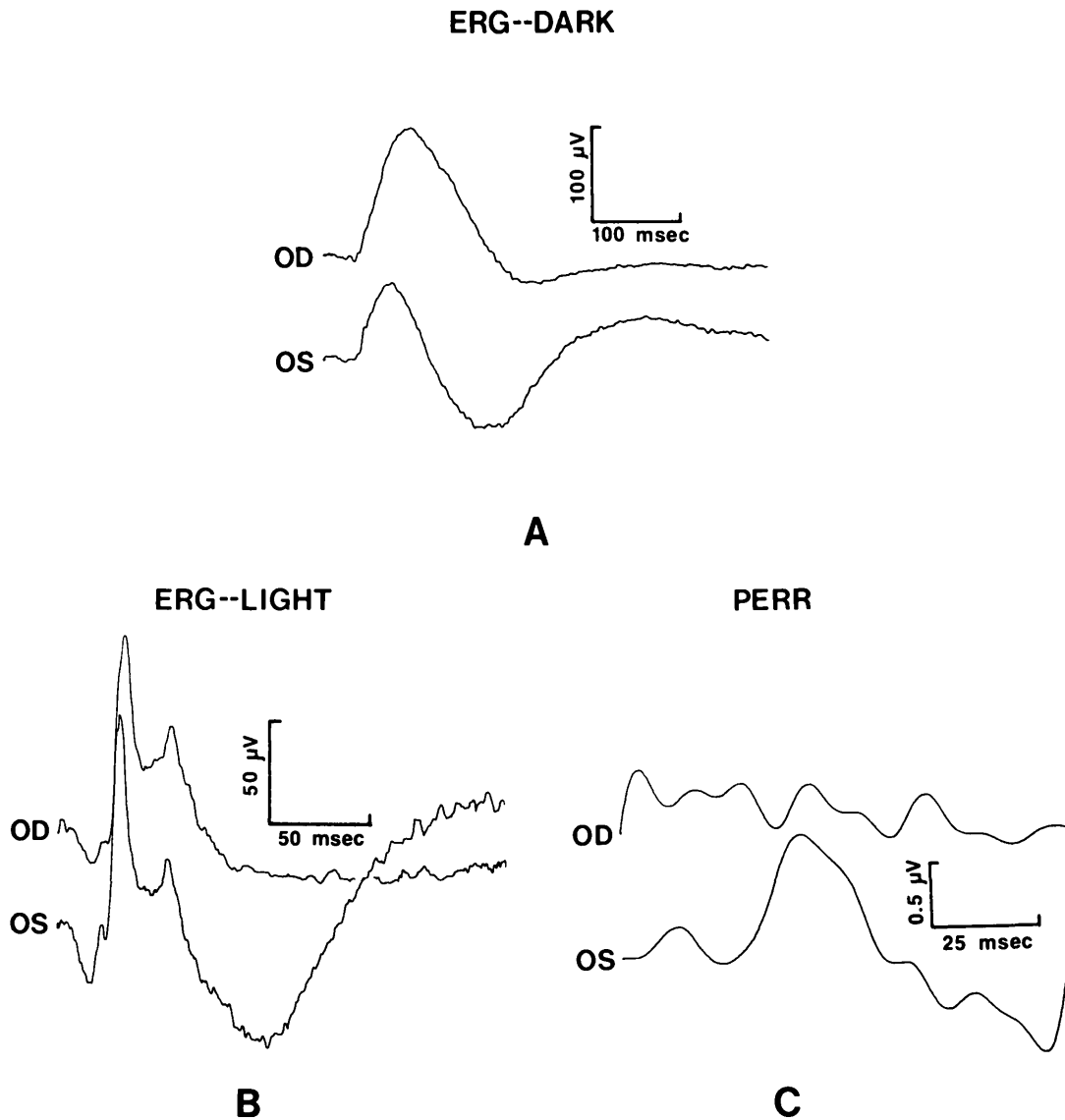


Fig. 2. Simultaneous recordings from the corneas with diffuse flash stimuli ($n = 20$) and patterns (PERR). **A**, After 15 min adaptation following the offset of a 1000 trolands field. **B**, After 4 min adaptation to 1000 trolands. **C**, Average after 1500 phase reversals of a stimulus pattern with 9 min arc (3.31 cy/deg) elements.

frequency. The characteristics of Fig. 1 were constant throughout all experiments. These were as follows: (1) sizable normal PERR and VER signals evoked by OS stimulation and (2) no measurable response by OD stimulation. Frequency doubling of the PERR signal was found uniformly. At low spatial stimulus frequencies the PERR exhibited an early, slightly negative component in the 20 to 30

msec range followed by a positive component about 50 msec from the previous phase alternation. Fig. 1, A, was recorded from each eye simultaneously; Fig. 1, B, was recorded from the scalp electrode while the contralateral eye was occluded. With such a large visual stimulus (40 min arc, 1.5 Hz), only 160 averages were required. PERR and VER amplitudes decreased at higher spatial frequencies. Time

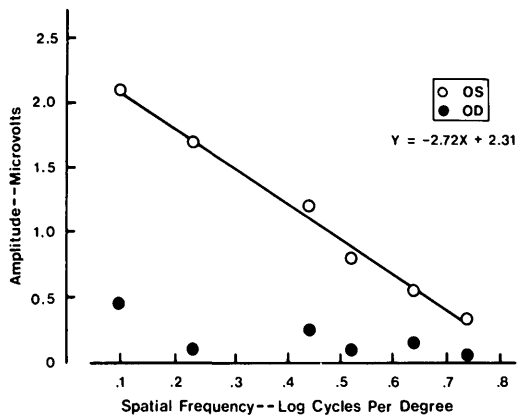


Fig. 3. Total power (F + 2F + 3F) at the PERR response fundamental frequency and its harmonics as it varies with the log transform of stimulus spatial frequency. The least-squares regression line and its equation are presented.

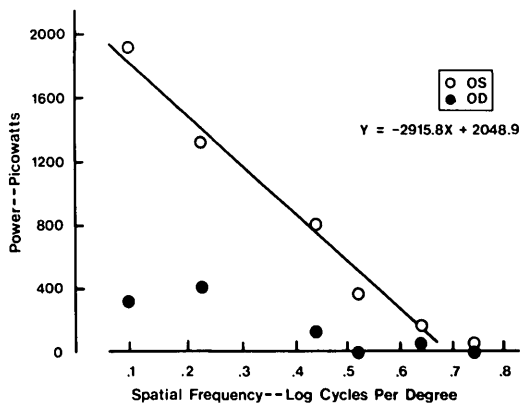


Fig. 4. Averaged response amplitude of the PERR as it varies with the log transform of stimulus spatial frequency. The least-squares regression line and its equation are presented.

for averaging became too great at 1.5 Hz. By inspection, the results at 1.5 Hz for larger cy/deg stimuli were similar to those at 3.5 and 8 Hz, which were fully analyzed. No OD response was present.

Fig. 1, A, is comparable to Fig. 2, C. Again the PERR was recorded from both eyes simultaneously. In this case, the stimulus was 9 min arc (3.3 cy/deg), the stimulation rate was 8 Hz, and the number of signals was 1500. There was no identifiable signal evoked by stimulation of OD. This is in marked contrast to the situation when the retina was stimulated by diffuse flash illumination. Here (Fig. 2, A and

Table I. Coefficient of determination (r^2) matrix for eye, PERR amplitude, power, latency (+/- peaks), and linear/log spatial frequency

cy/deg	Eye	Amplitude	Power	Latency	
				-	+
Linear	OS	0.79 ^A	0.88 ^B	0.90 ^B	0.49
	OD	0.59	0.69	—	—
Log	OS	0.97 ^C	0.98 ^C	0.86 ^A	0.38
	OD	0.52	0.62	—	—

Probability of underlying r: ^Ap < 0.05, ^Bp < 0.01, ^Cp < 0.001.

B), few differences were present between the two eye signals, particularly in the light-adapted condition. Even in the dark-adapted record (Fig. 2, A) there is no clear evidence of any pathologic condition in OD. In fact, most clinical laboratories would probably report that both eyes were electrically normal or near the limits of normal variability.

Across a span of spatial frequencies, Fig. 3 shows that the amplitude of the PERR measured from the OS varied in a highly consistent fashion. The response OD was rarely greater than the peak-to-peak noise level amplitude (approximately 0.25 μ V) that was recorded when the pattern was defocused. The lack of clear response in OD was marked to the extent that it was necessary to make the amplitude measure (Fig. 3) for OD at precisely the same latencies identified on the troughs and peaks of the OS signal elicited at that spatial frequency. No "characteristic" peaks or troughs were available as markers.

Because of the subjective nature of amplitude measurements in relatively noisy signals, the "fast" Fourier analysis can be applied to measure power density at the response fundamental (16 Hz) and some of its harmonics.¹⁷ The FM tape records were analyzed for absolute power density in picowatts. The power axis in Fig. 4 is power at the response fundamental (F) plus harmonics 2F and 3F. There was no apparent relationship between power at other frequencies and the stimulus spatial frequencies. The power spectrum measures did not alter the fundamental relationship between the OD response, the OS response, and the respective spatial stimulus frequen-

cies. The major gain appears to be that the power analysis results have an average (OS, 8 Hz stimulus) 12.6/1 signal/noise ratio, whereas the amplitude analysis has only an average (OS, 8 Hz stimulus) 2.07/1 signal/noise ratio.

The coefficient of determination,¹⁹ or r^2 , is an unbiased estimate of the extent to which the x-variable predicts the y-variable. It is based on the correlation coefficient (r). An r^2 matrix in Table I shows that the OD response is not a good predictor of stimulus spatial frequency. It is of theoretical interest that the data are fit best when spatial frequency is expressed as a logarithm and when it is plotted against power rather than amplitude. However, the differences in r between the log-transformed data and the linear data can be seen only in the third decimal place. The latency results uncovered by the r^2 matrix correspond with the timing of the PERR data, trough and peaks, when inspected. The timing of the positive peak that consistently occurred approximately 50 msec after the stimulus phase reversal appears to be relatively stationary and weakly linked to the stimulus spatial frequency. The early negative trough of the PERR between 27 and 36 msec is dependent on the spatial frequency of the stimulus.

Statistical probabilities and associated tests were not used to compare PERR production between OD and OS, since there was no overlap found between the two distributions. Calculation of the intercept values for the regression equations (OS, Figs. 3 and 4) yields 7.09 and 5.04 cy/deg, respectively. Converted to Snellen units (20/80, amplitude; 20/120, power), these become an estimate of spatial resolution threshold. Since OS was 20/20, there is an underestimation, which may be a result of the low stimulus contrast. Much better agreement with subjective threshold has been reported.¹⁷

Discussion

We have avoided the use of the term "ERG" when referring to the signal produced by the retina in response to counterphased pattern. The signals may have different origins.

In addition to the PERR, there are at least three major retinal signals that may be recorded with capacitive coupling from the cornea. All of these are ERG components and may be elicited by diffuse retinal illumination. Most of our understanding of these potentials and the cellular interactions that produce them originates in animal research. The origins of the a- and b-waves have been the most thoroughly studied. New perspectives and a literature review are provided by Rodieck³ and Brindley.²⁰ Recent research on b-wave origin⁵ and on origin and function of the minor components ("oscillations" or "fast potentials") support a glial-cell origin for the b-wave and identify the latter signals with information transmission in the amacrine cells and/or inner plexiform layer.^{8, 9} The activity of the ganglion cells has not been proposed as a contributor to the complex ERG signal (ref. 3, p. 556). The results of the animal studies have been largely consistent with the conclusions reached by researchers studying the human ERG. Karpe¹⁰ and Deutman²¹ propose that the human a- and b-waves arise from the receptor and intermediate (bipolar cell) layers of the retina. Examination of the minor components of the human ERG^{6, 7} relate these signals to photopic vision and innerretinal layers exclusive of the ganglion cells.

Our findings clearly separate the eyes of the subject on their ability to produce PERRs. At the same time, we substantiate that the more usual "ERG" potentials are present in both eyes. We find a near-identity of the eyes of our subject for the light-adapted ERG, a clearly hyperresponsive dark-adapted b-wave in the OD, and an absent PERR in the OD. The difference between the b-waves in dark adaptation is of theoretical interest because of the controversy about the presence of efferent fibers in the optic nerves of mammals. The controversy seems traceable to the report by Jacobson and Gestring²² that sectioning of the optic nerve selectively increases the b-wave amplitude. This could not be replicated by Brindley and Hamasaki,²³ who provide impressive arguments and data in support of the absence, in the cat, of an efferent system for retinal control. The arguments are summarized by Brindley,²⁰ who states that his posi-

tion on centrifugal fibers is "admittedly skeptical" (pg. 109). However, a summary by Wolter²⁴ provides new human data that add to a series of reports and lead to the conclusion that anatomically identifiable efferent fibers do exist in the human optic nerve. In the evaluation of the results we present here, one is reminded of this controversy and the all-too-frequent neglect of species differences.

The consequences of the lesion(s) of the visual pathway in this subject are key to the interpretation of the data. The clinical data clearly indicate a disconnection of the right eye from the central nervous system. The electrophysiologic data clearly indicate a deficit of a single stimulus-specific signal in that eye. Atrophy of the optic nerve is apparent, and James²⁵ categorically states "degeneration of the ganglion cell invariably follows serious injury to the axon." Interest in retrograde degeneration in the optic nerve and retina after lesions may be found in the old literature.²⁶ Many of the earlier investigators assumed that there is a temporally progressive change in the axon from the site of the lesion toward and finally involving the ganglion-cell body. Radius and Anderson²⁷ have questioned the concept of progressive retrograde degeneration and provide evidence for nearly simultaneous degeneration of the ganglion-cell body and its axon.

Ganglion-cell disappearance may be rapid. Radius and Anderson²⁷ report that in the primate retina, there is 75% loss of the ganglion cells 10 weeks after photocoagulation of some of the retinal vessels. James found only "occasional" normal ganglion cells 20 days after section of the rabbit optic nerve. After 120 days and from 150 slides, James²⁵ reported "four or five" cells that seemed to be small ganglion cells. In an article most closely related to our results, Kupfer²⁸ reported the pathologic findings in a human eye. He concluded that a lesion of the optic-nerve fibers at the level of the chiasm results in retrograde degeneration of the ganglion cells in 6 months.

Because the lesion in our subject occurred 15 months before our recordings were made and because there is no clinical or laboratory

evidence of information transmission in the right optic nerve in the presence of objective evidence of optic atrophy, we presume that a large majority of the optic nerve fibers and ganglion cells in that eye have degenerated. In none of the references on retrograde degeneration of the optic nerve have findings been cited to indicate more distal (trans-synaptic) degeneration in the retina. In fact, ophthalmoscopically and electroretinographically, the retina of our subject's right eye is normal. On the basis of the literature and our results, we conclude that the PERR of humans is highly dependent on or originates in the retinal ganglion cells.

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