Simultaneous ERG and VER in lesions of the optic pathway

Jerry H. Jacobson, Tatsuo Hirose, and Takashi A. Suzuki

The effects of clinical disease of the retina, optic nerve, chiasm, and cerebrum upon the electrical activity of the retina (ERG) and the brain, as recorded at the occipital surface (VER), have been studied and compared to those obtained from the surface of the brain of cats surgically prepared with similar lesions. In both situations it is possible to detect variations from normal in the responses recorded. The use of the intact opposite eye or hemisphere as a control is of value in increasing the significance of the findings. A sinusoidally varying stimulus seems in some instances a more discriminating test of abnormality of function than a square wave or flash stimulus.

The electroretinogram has proved itself to be of value as a diagnostic instrument, especially in those situations in which subjective testing is not reliable, as for example, in children. This phenomenon provides a means of evaluation of the status of the photopic and scotopic components of the retina as well as of the total retina.

The visual system, however, consists of more than merely the retina and, with the advent of superimposition and computer averaging techniques, which have made recording of the electrical activity of the brain (VER) evoked by light stimuli feasible, it has become of interest to determine the clinical applicability of these techniques. With objective measurements of occipital and retinal integrity, determination of the site of a lesion affecting vision should be facilitated. The occipital response, however, is technically more difficult to work with than the ERG because of its low amplitude, and intrinsically more variable because of such factors as attention and nonvisual stimuli. This is a report of our experiences with simultaneous recording of the electrical activity at the two sites.

Methods

ERG and VER were recorded with Grass disc electrodes 8 mm. in diameter placed at the center of the lower lid, and 2 cm. above and 3 cm. lateral to the inion, referred to the joined earlobes. A ground electrode was attached to the chin. Although the ERG observed with a lid electrode is of lesser amplitude than that obtained with a contact lens electrode, the wave form and the time relations of the a and b waves are the same as those with the contact lens, and allow location of the peak of each wave relative to VER components. Precise measurement of the amplitude of ERG, however, was made separately with the contact lens. Activity picked up from the left and right occiput and the lower lid were fed into the amplifiers of a Grass EEG machine, which had no filters in the circuit. Time constant was 0.125 seconds, and the characteristics of the amplifiers are flat from 1 to 1,000 cycles. The output of the

From the Cornell University Medical College, Department of Surgery (Ophthalmology), New York, N. Y. 10021.

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EEG machine was led to the computer of average transients (CAT) and a cathode ray oscilloscope, after passing through an amplitude equalizing and reducing circuit. Fifty to 300 responses were averaged and displayed on the screen. Individual responses were recorded from a cathode ray oscilloscope.

The photic stimulator is the same as that used by Nagata and Jacobson.24 Square wave light stimuli with durations of either 20 to 30 or 100 milliseconds were used at a rate of 3 cycles per second. There was no audible noise. The light stimulus was emitted from one end of fiber optics, 6 mm. in diameter, placed 7.5 cm. from the cornea of the stimulated eye. The light beam was in line with the visual axis.

Twelve subjects (10 men and 2 women, all right-handed) between 24 and 42 years of age served as normal subjects, and 33 subjects with visual disorders were studied. Pupils were maximally dilated with 10 per cent phenylephrine and 5 per cent tropicamide to avoid possible "habituation" due to change in pupil size.25 The subject lay supine with one eye open and the other covered with opaque material. He fixed the open eye at the center of the stimulus light in a dark, quiet, electrically shielded room.

Results

I. Normal VER. Two cm. above the inion at the midline, the VER consisted of several components. The initial occipital surface negative wave peak at 46 milliseconds, followed by surface positive, negative, positive, and negative waves, at 68, 115, 155, and 188 milliseconds, respectively (Fig. 1). Although the stimulus parameters, including duration and intensity, were different from those used by Ciganek,4 the basic patterns of these responses are similar to his results. These negative and positive waves were labeled I, II, III, IV, and V, according to Ciganek's designation. One additional pair of positive (VI) and negative (VII) waves usually follows the V wave, but these are not constant as to form and latency. Frequently, a small surface positive wave preceded wave I. Its peak lay at 18 to 32 milliseconds (Fig. 1, arrow). This may be similar to the wave which Cobb and Dawson56 described as the initial positive deflection. Rarely, this initial positive wave was further divided into two humps by an interposed small surface negative wave at about 24 milliseconds. The amplitude of each wave was measured from the peak or trough immediately preceding. As the electrode was moved laterally from the midline, waves I and II tended to decrease in amplitude. Wave III did not decrease, and at 3 cm. lateral, it achieved its maximum. Further lateral displacement tended to decrease its amplitude. Waves IV and V increased in amplitudes and became maxi-
mal 5 cm. lateral to the midline. A further lateral position decreased the amplitude. Along a parasagittal line 3 cm. lateral to the midline, the responses were largest between 2 and 4 cm. above the inion. Anterior or posterior to these the responses were smaller and their peaks delayed.

To record the VER from patients, we positioned the electrodes 3 cm. lateral to 2 cm. above the inion. Fig. 2 demonstrates the combined VER with this electrode position and ERG with several stimulus intensities of two different durations. The maximum intensity was $2.5 \times 10^{-5}$

*Fig. 2. VER from normal subject with different stimulus intensities and durations. Maximum stimulus intensity of neutral filters in stimulus path. Left column: 20 milliseconds duration stimulus. First and second traces, VER from ipsilateral and contralateral occiput (3 cm. lateral to 2 cm. above inion), respectively. Third trace, ERG. Fourth trace signifies stimulus shape and calibration of 1 microvolt for VER and 5 microvolts for ERG. Left column: 100 milliseconds' duration stimulus. First trace, VER of contralateral occiput. Second trace, ERG. Third trace, stimulus shape and calibration 1 microvolt for VER, 5 microvolts for ERG. Negativity of occiput (VER) and positivity of lower lid (ERG) produce upward deflection. Two hundred and fifty responses averaged.*
foot-lamberts. The figures at left indicate density of neutral filters placed in the stimulus path. The topmost trace of each group is the VER from the ipsilateral occiput and the second from the occiput contralateral to the stimulated eye. The third trace is the ERG, picked up from the lower lid of the same eye. The lowest trace is a calibration signal and a record of time of stimulus. Two hundred and fifty responses were averaged.

The left column consists of responses to 20 milliseconds’ duration stimuli. As the stimulus intensity increased, the peak time of each component decreased. Wave I and the initial positive wave became apparent at the intensity of -1.0. Further increase of the intensity above -0.5 did not produce increased amplitude of response, but the II wave was divided into two parts by the interposition of a negative wave (Fig. 2, -0.3, arrow). This negative wave was most prominent with 0.0 stimulus. The right VER was complicated by multiple humps between peaks of I and III (Fig. 2, 0.0, arrows). The interval of these peaks was 7.5 to 10 milliseconds, corresponding to the “on rhythms” reported by Yokoyama, who has found a close relation of on rhythms to the oscillatory potential of the ERG. Others have observed similar waves. The amplitudes of the VER was almost equal in the two hemispheres, although III and IV waves of the contralateral VER tended to be larger than those of ipsilateral VER. On rhythms could be recognized only in the contralateral response under these conditions. These findings agree with those of others. Asymmetry of peak time of I to III waves was not common among normal individuals, although interindividual differences of VER were present. The initial positive wave was observed in 20 per cent; I wave, 60 per cent; II wave, 91 per cent; III and IV waves, 100 per cent; and V wave, 85 per cent of normal persons. The peak times of the initial positive wave, I, II, III, IV, and V waves were 18 to 38, 45 to 60, 50 to 80, 70 to 120, 125 to 155, and 140 to 200 milliseconds, respectively.

With intense stimulus and stimulus duration of 100 milliseconds (Fig. 2, right column, 0.0), the VER exhibited rhythmic humps, regularly spaced, with 30 to 32 milliseconds’ peak to peak intervals, starting at 49 milliseconds and persisting until 220 milliseconds after the onset of stimulus. A small negative hump preceded the first wave of these rhythmic humps. We have tentatively called these rhythmic humps “undulations.” The undulations were often recorded with stimuli of shorter duration than 100 milliseconds. In Fig. 2, for example, left column, 0.0, the first trace has this rhythmic tendency. Thus the undulations are not limited to long duration stimuli. The production of the undulations may not be ascribed to the change of the basic pattern of the background EEG. At the time of recording, the α-wave was blocked by light, by the fixation of the eye, and by constant attention to the stimulus light, and the EEG was typical of an alert state. With the pattern of EEG unchanged, less intense stimulation of shorter duration did not produce undulations. However, we cannot exclude possible relationship of these humps to a basic EEG pattern. A series of rhythmic waves of VER in animal experiments has shown some relations to the EEG pattern. The undulations we observed are not the so-called rhythmic after-discharge, since the latter has a lower frequency similar to the α-wave, and is usually seen much later after the stimulus onset than the undulations. The undulations are not identical with the on rhythms reported by Yokoyama, since the latter has a lower frequency similar to the α-wave, and is usually seen much later after the stimulus onset than the undulations. The undulations have the same physiological significance as I to V waves, although the peaks of some of the humps may temporally coincide with those of I-V waves. The normal human VER components known thus far are: (1) initial positive wave, I, II, III, IV, V, VI, and VII waves; (2) rhythmic after-discharge:
8 to 12 cycles per second; (3) on rhythms: 100 to 200 cycles per second; and (4) undulations: 31 to 34 cycles per second.

II. Pathology of VER and ERG. In order to begin to study the effects of disease upon the VER we performed two types of study. One of these was a study of the effects of surgically induced lesions of the optic nerve, the chiasm, and the optic tract in cats and the second a study of the effects of human disease processes verifiable by other techniques.

1. Experimental studies. Fig. 3 demonstrates the result obtained in each of 3 cats studied. In each instance the animal was immobilized and under local anesthesia. Recordings were from the area of maximum response in the cortex of normal cats. If one optic nerve is cut, no occipital response is evoked by stimulation of that eye. If the chiasm is cut longitudinally, no contralateral response was obtained, while a normal ipsilateral response was found. Interruption of the optic tract eliminated the response from that hemisphere.

2. Clinical studies. With these experimental findings in mind, patients with lesions at various sites were studied.

A. Retinal disease. Patient 1, a 35-year-old man with retinitis pigmentosa, had had poor night vision for 15 years (Fig. 4, J. C.). Fundi revealed normal discs and retinal vessels of normal caliber. A good macular ring and foveal reflex was present in both eyes. Clumps of spidery black pigment were found about and on the retinal vessels in the equatorial region. ERG was nonrecordable with lid or contact lens electrode. VER revealed definite I to V components of reduced amplitude. The III wave, in normal subjects the most prominent component, was especially affected. The peak of each wave lay within normal temporal range.

Patient 2, a 21-year-old man with retinitis pigmentosa, had been aware of poor night vision as long as he could remember (Fig. 5, M. R.). His fundi had waxlike white-yellow discs with relatively well-defined margins and attenuated vessels.

Fig. 3. Cortical responses from surface electrodes on cat cortex at site of maximum response in normal cat and in animals with surgical lesions at sites indicated.
Fig. 4. Patient 1. Patient with mild retinitis pigmentosa. Vision is corrected visual acuity. Dark adaptation curve obtained with Goldmann-Weekers adaptometer after preadaptation of 2,000 lux for 5 minutes. Absolute threshold for light measured 15 degrees above fovea. Top pair of records with 30 milliseconds' stimuli, center with 100 milliseconds' stimuli, lowest pair obtained with all conditions the same but eyes shielded from stimulus, as control.

Fig. 5. Patient 2. Findings in severe retinitis pigmentosa.
Clumps of bone corpuscle-shaped black pigment were present at the equatorial circumference. ERG was nonrecordable in both eyes with lid and contact lens electrode. VER was present but greatly reduced, consisting only of late positive wave.

Of 6 other cases with retinitis pigmentosa and nonrecordable ERG, 2 had nonrecordable VER, 2 had no I to III waves with small IV and V waves, and 2 had reduced amplitude of all waves of I to V. Those cases which had no VER were advanced cases, both showing optic nerve atrophy.

This variability of VER findings is in agreement with those reported by others.5, 17, 31, 32

Patient 3 (Fig. 6, M. S.) had occlusion of the central retinal artery; she had had acute loss of vision for 10 days in her left eye and 23 days in her right prior to examination. She was only able to detect hand movements in the temporal field of the right eye. Fundi revealed edema of both retinas with a cherry red spot at each

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M. S. Age 70 Female
Diagnosis: Bilateral occlusion of central retinal arteries
Vision: L-L. P., R-H.M.
Lesion

Fig. 6. Patient 3.

R. S. Age 45 Male
Diagnosis: Bilateral acute retrobulbar neuritis
Vision: L- H. M., R- H. M. (temporal field)
Lesion (suspected)

Fig. 7. Patient 4.
macula. Retinal arteries were extremely attenuated and discs pale with blurred margins. No pulsation of the vessels appeared with pressure on the globes. The ERG with the contact lens electrode showed a deep a wave with subnormal b wave in both eyes, but the b wave of the right was not as much depressed as that of the left. VER in response to left eye stimulation revealed very small amplitude of I, II, and III waves with peak times much delayed. L-VER to right eye stimulation showed almost normal I to V waves, while R-VER gave only small I and II waves with their peak times slightly delayed. The presence of the well-developed contralateral VER to the right eye stimulation agrees with the subjective evidence of a remaining relatively intact visual island on the nasal part of the retina.

B. Optic Nerve Disease. Patient 4 had acute retrobulbar neuritis (Fig. 7, R. S.). The patient had had loss of vision of short-term onset for 20 days in the right eye and 19 days in the left eye prior to examination. Patient's vision had been reduced to no light perception in both eyes but had recovered to the point of hand movements in the temporal field of each eye when seen. His fundi revealed both discs of normal color, with slightly blurred margins. The retinal veins were engorged. No exudate or hemorrhage was observed. ERG of each eye was normal. The L-VER with stimulation of either eye was of extremely low amplitude with normal peak times. R-VER to the left eye stimulation had small amplitude of I, II, III, IV, and V waves with peak times delayed. R-VER to right eye stimulation had only small delayed III, IV, and V waves.

Patient 5 had optic nerve atrophy (Fig. 8, B. R.). At the age of 12 the patient noted failing vision and ataxia. He was found to have hydrocephalus secondary to aqueductal stenosis. He was operated upon (Torkildsen shunt) at 13 years of age, and developed staphylococcus meningitis secondary to wound infection. This was treated with antibiotics and ventriculopleural shunt. When seen, the pupillary response to light was sluggish, the fundi were tesselated with pale discs and well-defined margins. The macular ring and foveal reflex were absent, but the retinal vessels were within normal limits. ERG was normal in both eyes, VER showed only a trace of I to V waves from L-occiput to the left eye stimulation without significant peak time delay. Eleven other cases of severe optic nerve atrophy or optic neuritis had similar findings: reduced am-

Fig. 8. Patient 5.
M.S. Age 46 Female
Diagnosis: Bitemporal hemianopsia
Vision 20/200
Lesion (suspected)

Fig. 9. Patient 6.

C.A. Age 88 Female
Diagnosis: L-Homonymous hemianopsia
Bilateral incipient senile cataract
Vision 20/40
Lesion (suspected)

Fig. 10. Patient 7.
plitude of VER and normal or delayed peak times. Reduction of the amplitude was not always accompanied by prolongation of peak times.

These findings confirm those of others.

C. CHIASMAL LESION. Patient 6 had bitemporal hemianopsia without macular sparing (Fig. 9, M. S.). A diagnosis of acromegaly had been made 18 years before our examination. She received radiation to the pituitary gland with arrest of progress of symptoms. One year before the examination the size of her feet and jaw increased and she underwent yttrium 90 implantation, resulting in bitemporal hemianopsia with decreased vision. Fundi revealed pale discs with well-defined margins, and retinal vessels within normal limits. ERG was normal in both eyes. There was a small VER on the side ipsilateral to the stimulus, and much-reduced or absent contralateral VER.

D. GENICULOCALCARINE LESIONS. Patient 7 had homonymous hemianopsia with macular sparing (Fig. 10, C. A.). A few weeks prior to examination the patient noted not seeing objects on the left, with no accompanying systemic symptoms. She had had a stroke previously, resulting in left hemiparesis several months before, and had hypertension and arteriosclerosis. Fundi revealed normal discs with early arteriosclerotic changes. ERG was within normal limits. L-VER were normal. R-VER with the left eye stimulus revealed larger I wave than that of L-VER. The descending branch of I wave was so gradual that it was difficult to locate the peak of II wave. R-VER to the right eye stimulation gave normal I wave and a little smaller II and III waves. The peak time of II and III of the R-VER were delayed to such an extent that they coincided temporally with that of III and IV, respectively, of the L-VER, giving an impression of reverse polarity of the response.

Six other cases with homonymous hemianopsia with macular sparing (about 3 > 7 degrees with 5/1000 white object) showed similar findings on the side of the involved hemisphere: A normal or slightly higher amplitude and mostly normal but occasionally delayed peak time of I wave; normal or below normal to absent response of II wave with peak time usually delayed; and small or absent III wave, the peaks of which were generally delayed. Gross asymmetry of the left and right VER is characteristic. These findings are in agreement, generally, with a number of other reports.

In some cases of incomplete homonymous lesions the difference in the response between the presumably diseased hemisphere and the normal is not striking. In an attempt to refine our techniques, we utilized as a stimulus a light source varying in intensity in a sinusoidal manner about a mean value. A considerable volume of experimental work with this type of stimulus has been carried out by psychologists, and it has several reasons for being of potential clinical value. The first of these is that it is a less drastic stimulus than one which goes on and off in a square wave manner, since visual perception is dependent upon the rate of change of the stimulus. There is experimental evidence that the occipital response to a light stimulus is "saturable," that is, that a maximum amplitude exists no matter how bright, or effective, the stimulus may be. Thus, if one considers a patient with a lesion of one hemisphere, a stimulus just adequate to evoke a maximum response in the normal hemisphere might be expected to evoke a somewhat lesser response in the diseased hemisphere. If, however, a stimulus of efficacy greater than liminal adequacy is used, it may drive the intact portion of the diseased hemisphere to produce a response equal to that of the normal, maximally responding hemisphere. Thus, using a less drastic stimulus, such as a sine wave, may detect a difference not visualizable by use of a square wave.

This sort of stimulus has other advantages—it is possible to vary the frequency and the depth of modulation and hence

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the stimulus intensity while maintaining a constant level of adaptation in the retina, since the stimulus is varying about a mean level.

An example of the clinical studies which indicate that this may be a valuable tool is shown in Patient 8 (Fig. 11). This 50-year-old man has a partial homonymous hemianopsia. With square wave stimulation there is no essential difference in the response between the two hemispheres. Fig. 12, however, recorded with a sinusoidally varying stimulus at 20, 40, and 80 per cent modulation depths, indicates a significant difference between the two hemispheres, the response in the right hemisphere being of clearly less amplitude.

E. WIDESPREAD INTRACRANIAL PATHOLOGY. One month prior to examination Patient 9 (Fig. 13, C. J.) noted sudden onset of unsteadiness of gait, followed by decreasing vision. Bilateral blindness was observed 3 weeks prior to examination. Hyperreflexia generalized. Spinal fluid Papanicolaou suggested neoplasia. Pneumoencephalogram showed dilatation of both ventricles consistent with cerebral atrophy. He died 2 weeks after our examination. Postmortem examination revealed primary carcinoma of right lung with metastatic adenocarcinoma to brain, meninges, and hydrocephalus. Ocular finding at the time of VER test showed no pupillary reflex to light and fundi within normal limits. ERG was normal in both eyes; VER was not detected. Two other similar cases had similar ERG and VER findings, as have the patients of others.17

Summary and conclusion

1. ERG and VER were recorded simultaneously with a rectangular light stimulus. The VER of the normal subject with 20 to 30 milliseconds' duration stimuli consisted of an initial surface positive wave with peak time of 18 to 38 milliseconds after the onset of stimulus followed by negative (I), positive (II), negative (III), positive (IV), and negative (V) waves at 45 to 60, 50 to 60, 70 to 120, 125 to 155, and 140 to 200 milliseconds, respectively. With differing stimulus conditions, oscillations having a 7.5 to 10 milliseconds peak-to-peak interval and other rhythmic humps of 30 to 31 milliseconds peak-to-peak intervals were observed.

2. Of 8 cases of retinitis pigmentosa, with nonrecordable ERG, 2 had nonrecordable VER, 2 had no I to III with small IV and V, and 4 cases had reduced, small amplitude waves I to V. Nonrecordable VER was associated with an atrophy of the optic nerve.

3. In occlusion of the central retinal
Fig. 12. Patient 8. Same patient as Fig. 11, sine wave stimulus at modulation depth indicated. Left column: left eye stimulated. Right column: right eye stimulated. Top trace each group from left occiput, center from right occiput. Lowest trace of each group 5 microvolts calibration and stimulus wave form record.

Fig. 13. Patient 9.
artery VER was of reduced amplitude of I to III, and the peak time was delayed.

4. Patients with optic nerve neuritis and optic nerve atrophy had reduced amplitude of VER with normal or delayed peak times and normal or upper normal limit ERG responses.

5. A patient with bitemporal hemianopsia without macular sparing had little or no contralateral VER and definite ipsilateral VER with normal ERG.

6. Patients with homonymous hemianopsia with macular sparing showed normal or slightly increased amplitude of I wave with usually normal but occasionally delayed peak time, normal or below normal amplitude of II with delayed peak time, and absent or reduced amplitude of III wave with much delayed peak time in the involved hemisphere as compared to the other hemisphere.

7. Widespread intracranial pathology is associated with nonrecordable or almost nonrecordable VER from both hemispheres and normal ERG.

8. Sinusoidal stimulation seems in some instances to be a more delicate detector of abnormality in the VER than a square wave stimulus.

9. Although individual differences do exist between the VER patterns of normal humans, the major components (II to IV waves) were present and constant in 85 to 90 per cent of those individuals studied. Using the record obtained from one hemisphere as a control against that of the other and the study of the responses elicited by stimulation of one eye as opposed to the other are of importance in increasing the validity of observed variations from normal responses.

REFERENCES


