

# Visually evoked responses in multiple sclerosis<sup>1</sup>

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**SUMMARY** Visually evoked cerebral responses (VERs) from the occipital and central areas were compared between 50 patients with multiple sclerosis and 50 control subjects. The average peak latencies of four occipital components (OII-OV) and two central ones (CIV and CV) were significantly delayed. In no instance was the amplitude significantly different. Routine EEGs were either entirely normal (16) or showed only minor findings (10) in 26 patients. Of this group, nine showed abnormal VERs. Seventeen patients had clinical symptoms or signs which pointed to spinal cord involvement only; nonetheless, eight in this group had abnormal responses. Inasmuch as changes in visually evoked potentials are not directly dependent upon the presence of a demonstrable field defect, the technique may be useful in detecting otherwise occult cerebral lesions.

Because multiple sclerosis frequently produces visual defects, it is natural to anticipate concomitant changes in visually evoked cerebral responses. However, a preliminary study of a small group of patients revealed that, while there were evident changes in some patients, they were not necessarily those having signs of involvement of the visual system. In the present study, an expanded sample of patients with multiple sclerosis was examined in order to ascertain (1) the effect of the disease upon the latencies and amplitudes of visually evoked waves, (2) the proportion of patients who have clearly abnormal responses, (3) the clinical correlates, if any, of the alterations, and (4) their relation to routine electroencephalographic findings.

## SUBJECTS AND METHODS

Visually evoked responses (VERs) were obtained on 50 patients with multiple sclerosis (35 females, 15 males) and 50 normal subjects (35 females, 15 males). The two samples were matched with respect to age (averages of 40.2 years each). Control subjects were in good health, without neurological illness, and not on any medication. All patients were hospitalized during a period of exacerbation of their disease. The final diagnosis of multiple sclerosis was made in each case by the Neurology Service.

The same procedure was followed in all subjects and patients. A resting EEG was obtained along with the evoked response study. The face of a Grass PS-2 photic stimulator lamp enclosed in a double walled box was placed 5 cm before the open eyes. No responses were detectable in control runs with the light covered. Background light intensity was adjusted to approximately one foot candle.

Routine EEGs were run on a Grass Model III Electroencephalograph. The evoked responses were summated with the Mnemotron Computer of Average Transients. Three computer runs were obtained. The averaging period for the first two runs was 250 msec and for the third was 125 msec. Light flashes were randomized and given one every 4 to 6 sec to a total of 50 for the first two runs and one every 0.5 to 1 sec to a total of 300 for the third run.

During the first run, data were obtained from the following electrode positions: left and right frontal, central, occipital, and temporal areas. The reference was joined-ears. Occipital electrodes were placed 3 cm above and 3 cm lateral to theinion. Central electrodes were placed 4 cm from the midline in the interaural plane. Data from the second and third computer runs were used to substantiate the initial observations and further to assess possible ocular and myogenic artefacts. The summated responses were displayed on a Tektronix cathode ray oscilloscope and photographed with a Hathaway oscilloscope camera.

Individual components of the evoked responses from the occipital and central regions were used for analysis. Both left and right-sided measurements were obtained with the left-sided values being used for statistical analysis (Kooi, Güvener, and Bagchi, 1965). The first five major occipital waves in either a negative or positive direction after the stimulus were studied. The vertex sharp wave

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(CV), a surface-negative deflection, was evaluated from the central response. The preceding positive wave (CIV) was also studied. Ranges for latencies and amplitudes of these occipital and central components are based on previous studies by Kooi and Bagchi (1964) and Kooi *et al.* (1965), and the control data obtained from the present study. CIV and CV were not measured if the eye blink artefact extended into the central regions.

Amplitude orders were established for the major components of the occipital and central response in the patient and control groups. Waves having the greatest, second greatest, and third greatest amplitudes in both negative and positive directions were identified and their latencies plotted (Fig. 1A and B and Fig. 2A and B).

The first major wave of the normal occipital VER is a surface-negative deflection (OI) having a general latency range of 30-70 msec. As seen from Fig. 1A, 2 clusters of latencies fall within the general range of OI. The intermediate wave previously described by Richey, Kooi, and Waggoner (1966) is responsible for the second of these. The next major deflection is a surface-positive one (OII) with a latency of 50-100 msec, a second surface negative deflection (OIII) with a latency range of 70-125 msec, then a second surface-positive component (OIV) having a latency range of 100-150 msec, and, finally, a surface-negative deflection (OV) with a latency range of 125-190 msec. Later occipital components were not measured and evaluated statistically. Latency ranges of CIV and CV are 95-115 msec and 110-165 msec respectively. These 2 deflections are seen in Fig. 2A. Earlier central components were also not evaluated statistically.

Latency was determined by measuring the interval between the instant of the stimulus and the peak of the appropriate major deflection within each range. Amplitude for the first occipital component was measured from the averaged base line to the peak of OI. For each succeeding component, in both occipital and central regions amplitude was determined by measuring from the peak of the preceding wave to the peak of the wave being measured. In a few instances, one or more components could not be identified. Measurements of selected waves in occipital and central regions have shown high orders of reliability in earlier test-retest studies with correlation coefficients of .91 to .96 for latencies and of .87 and .97 for amplitudes. Reproducibility is enhanced through the use of eyes-open technique which reduces variance from 'background' activity as well as factors related to the structure of the eyelids.

The VER was classified as abnormal if there was (1) absence of discernible response, (2) a unilateral absence or a left-right voltage difference of greater than 75% of one or more waves in homologous areas, or (3) a distinct left-right asymmetry of form confirmed by a difference in peak latency of the wave of more than 15 msec in homologous areas, or (4) in the case of CV, an absolute latency exceeding 170 msec (Kooi and Bagchi, 1964; Kooi *et al.*, 1965). Three of the normal controls had responses which met these criteria, all because of asymmetries of form.

## RESULTS

Twenty-six of the 50 resting EEGs in the patient

group were either entirely within normal limits or showed only borderline non-specific findings. Twenty EEGs showing primarily theta or theta-delta patterns in the temporal regions were classified as mildly abnormal. Three records were interpreted as moderately abnormal because of an excess of slow components in the background pattern plus temporal theta-delta transients. One record was markedly abnormal because of a slow background pattern (7-8 Hz) plus delta activity shifting between the temporal regions. In no case were spikes or spike-wave discharges seen.

Figures 1 and 2 show the peak latencies of the major waves in occipital and central regions selected according to relative amplitude in control and patient groups. By inspection there is more variability in the patient group with a resultant lack of definition of the clusters representing each of the major components previously described.

Table 1 shows the analysis of average latencies for the five occipital and two central components. Every component shows a statistically significant delay in the patient group with the exception of OI. Further statistical evaluation revealed that the latency of OI was not significantly different in the patients and controls when the patient group was restricted to the 18 cases with visual signs—central scotomata (11), enlarged blind spots (four), homonymous field defects (three), optic atrophy (two), bilateral nonhomonymous field defects (one).

Although there was considerable variation in amplitudes throughout the patient group and many individual cases showed definite left-right amplitude asymmetries of one or more components, in none of the statistical comparisons of either the right or the left side were average amplitudes of the five occipital or two central components statistically different from comparable components in the control population. When patients with and without visual system damage were compared, no significant differences emerged between average latencies or amplitudes of any of the seven components studied.

Figure 3 shows typical central and occipital responses in a normal subject.

Figures 4 to 6 are examples of the evoked response in the central and occipital regions of three multiple sclerosis patients.

Table 2 shows a comparison between all cases of multiple sclerosis versus cases by neurological categories in respect to incidences of normal VERs. The proportion of deviant responses was not significantly different in the group of 18 patients who had evidence of visual system damage as compared with the group as a whole. The 10 brain-stem dysfunction cases showed primarily dissociative nystagmus. Of five patients presenting with an organic mental

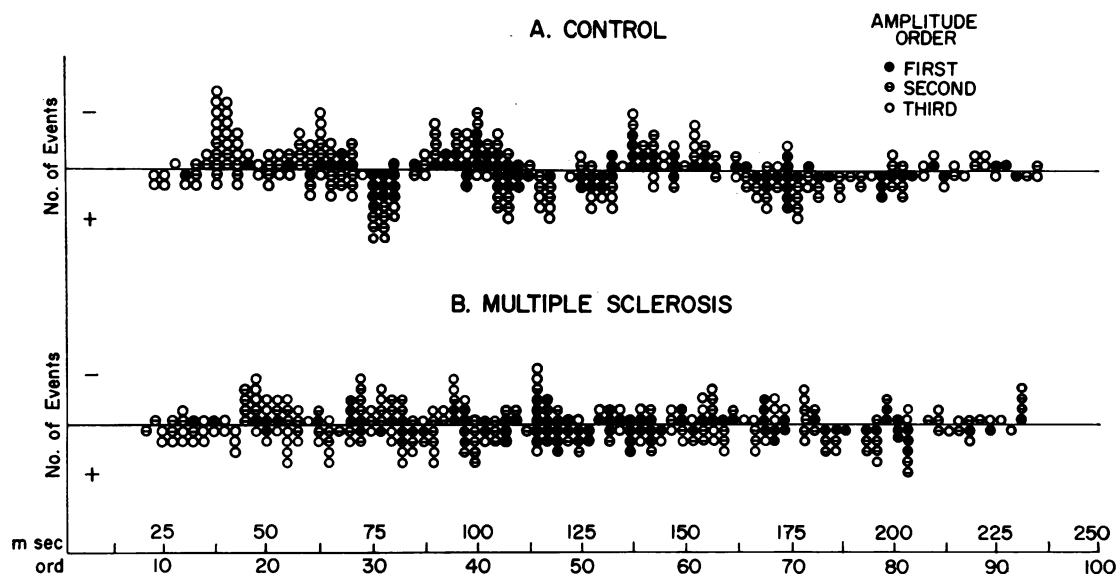


FIG. 1. Amplitude orders and latencies of major waves in the occipital region, three surface-negative and three surface-positive for each subject. A: control subjects,  $N = 50$ . B: patients with multiple sclerosis,  $N = 49$ . Note that the individual components (latencies given in text) are not well delineated in the patient group.

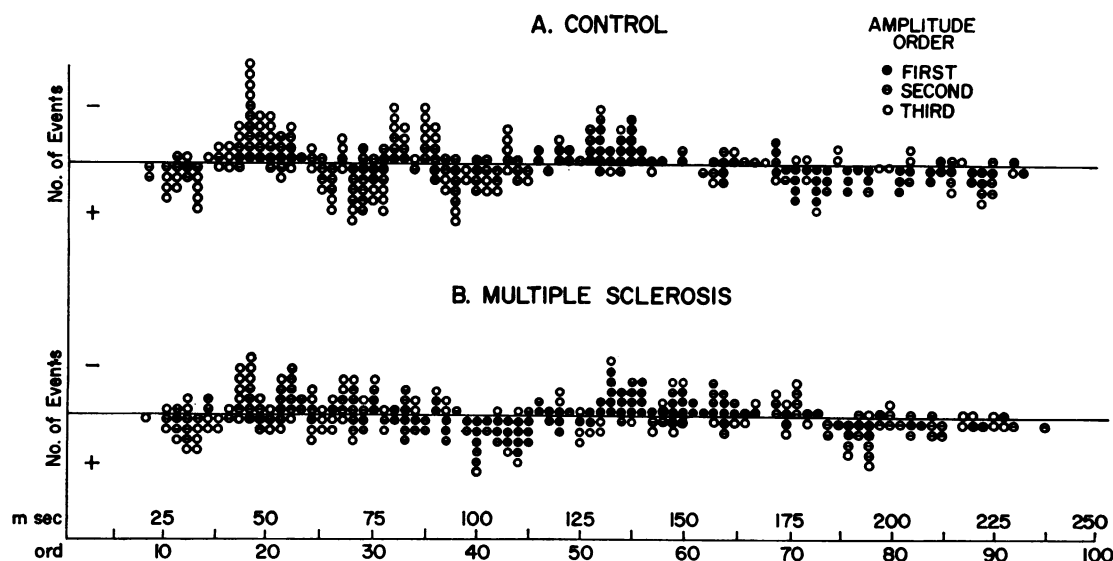


FIG. 2. Amplitude orders and latencies of major waves in the central region, three surface-negative and three surface-positive for each subject. A: control subjects,  $N = 46$ . B: patients with multiple sclerosis,  $N = 49$ . (See under Fig. 1.)

TABLE 1  
AVERAGE LATENCIES OF VERs IN PATIENT AND CONTROL GROUPS

	OI		OII		OIII		OIV		OV		CIV		CV	
	(msec)	(no.) <sup>1</sup>	(msec)	(no.)	(msec)	(no.)	(msec)	(no.)	(msec)	(no.)	(msec)	(no.)	(msec)	(no.)
Multiple sclerosis	52.5	44	81.8	45	105.5	46	132.8	44	160.5	40	114.5	49	151.8	49
Control	51.3	50	75.3	49	95.3	49	118.0	47	148.0	47	103.5	42	136.0	46
t		.48		2.23		3.52		4.77		3.50		3.62		4.31
P				<.05		<.001		<.001		<.001		<.001		<.001

<sup>1</sup>No. of individuals.

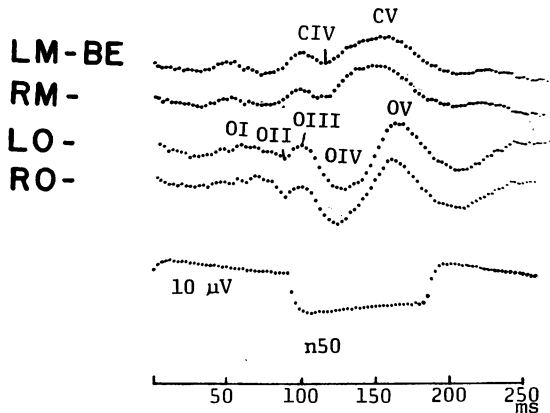


FIG. 3. Typical responses in the central and occipital regions of a normal subject (F26). The seven waves evaluated in this study are indicated.

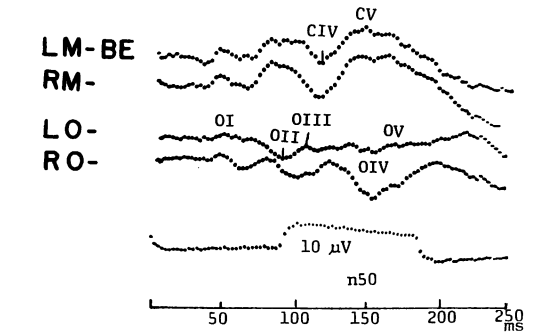


FIG. 4. The two central components in this multiple sclerosis patient (F30) were normal. Note the delay of OIII on the left side.

syndrome, four had deviant responses. One of the four, who also had bilateral optic atrophy, had no detectable evoked response but showed a normal resting electroencephalogram and a normal electro-

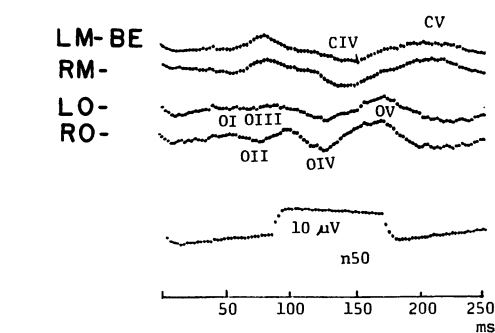


FIG. 5. This patient (M45) shows considerable delay of the two central components with CV occurring at 200 and 207.5 msec on the left and right sides respectively. There is also a slight latency and amplitude asymmetry of OIII. This patient had a mild organic mental syndrome.

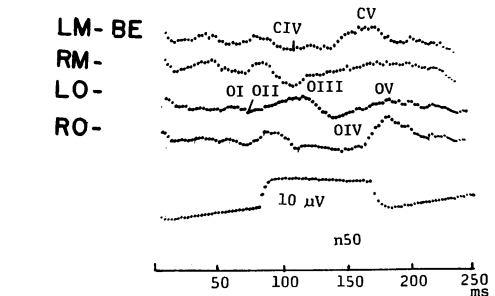


FIG. 6. In this patient (F26) there is an asymmetry in culmination of CV with the delay occurring on the right side. Also, note asymmetry of OIII with this component being delayed on the left side.

retinogram. The remaining three had delayed culmination of CV. It is noteworthy that eight patients who had spinal cord signs only showed abnormal evoked patterns. Three patients of the

TABLE 2  
VERs IN MULTIPLE SCLEROSIS

	All cases (n = 50)	Categories by neurological signs <sup>1</sup>			
		Visual (n = 18)	Brain-stem dysfunction (n = 10)	Organic mental syndrome (n = 5)	Spinal cord signs only (n = 17)
VERs					
Normal	30	10	8	1	9
Abnormal	20	8	2	4	8
Types <sup>1</sup>					
Absent VER		1	0	1	0
L-R amplitude difference >75 %		3	1	1	1
L-R latency difference >15 msec		6	0	1	3
Latency CV >170 msec		5	2	3	5

<sup>1</sup>Not mutually exclusive.

eight had normal resting electroencephalograms. The EEG results are compared with the VERs in Table 3.

TABLE 3  
VERs AND EEG FINDINGS

	EEG	
	Normal	Abnormal
VERs		
Normal	17	13
Abnormal	9	11

#### DISCUSSION

It appears that multiple sclerosis commonly affects photically-induced cerebral responses, the average latency of every component examined except OI being significantly delayed. Moreover, the changes were of sufficient extent to be considered abnormal in 40% of the patients as compared with 6% in a control group. The fact that significant deviations occur in patients who, from a clinical standpoint, have evidence of only spinal cord involvement or who have normal resting electroencephalograms, or both, points to areas of potential clinical application.

The apparent lack of relationship between clinical evidence of involvement of the visual system and changes in the VER, especially in respect to the early occipital components, warrants comment. Cigánek (1961) called the first three occipital waves the primary response and assumed them to be evoked by a stimulus following the specific pathway. Kooi *et al.* (1965), in studying patients with and without homonymous field defects, found alterations of the response with but few exceptions in the former group, disturbances in the latencies of OI and OII being the most characteristic change. These

earlier results, taken together with the present findings, suggest that cortical responses elicited by diffuse binocular photic stimulation are more likely to be distorted by central than by peripheral lesions of the visual pathway. In keeping with this is the fact that both patients in the present series with homonymous field defects had deviant VERs. Questions remain, however, as to the importance of such factors as size of the visual defect and its location within the visual field.

It is evident from our data that alterations of the VER occur commonly in patients who have no evidence of visual pathway damage whatsoever, suggesting that conduction defects within non-specific cerebral or, more strictly, non-primary pathways may be responsible for some of the observed deviations. In this connection, however, it is pertinent to consider another line of reasoning which offers an alternative explanation for the dissociation between the clinical signs and electrical phenomena. It has been shown in cases recovering from an acute exacerbation of the illness in which the somatosensory system has been affected that the configuration of the cerebral response to nerve stimulation may continue to improve after sensory function has returned to apparent normality (Baker, Sances, and Larson, 1966; Namerow, 1968), suggesting the presence of mechanisms that compensate for disturbances of nerve transmission attendant upon lesions directly within the primary sensory pathway. Without prejudice to this theory, which may well be applicable in certain instances, our group data would not seem to be satisfactorily viewed in this light, inasmuch as no appreciable differences were found between patients with and without overt signs of involvement of the visual pathway.

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