

Visual and somatosensory evoked cortical potentials in multiple sclerosis

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SUMMARY The diagnostic value of the pattern reversal evoked cortical potential (VEP) and the somatosensory evoked cortical potential (SEP) has been compared in 50 patients with established or suspected multiple sclerosis. A prolonged latency of VEP was found in 96% of definite cases of multiple sclerosis, 58% of probable cases, and 20% of possible cases. A prolonged latency of SEP by stimulation of the median or peroneal nerves or both was found in 86% of definite cases of multiple sclerosis, 83% of probable cases, and 50% of possible cases. When combining the results of all three tests the diagnostic yield increased to 100%, 92%, and 50%, respectively.

Since the introduction of the technique for recording cortical evoked potentials stimulated by pattern reversal as a supplementary aid in diagnosing multiple sclerosis, providing objective evidence of even clinically silent lesions by Halliday *et al.* (1972, 1973b), there have been several attempts to reproduce their positive results (Asselman *et al.*, 1975; Lowitzsch *et al.*, 1976; Mastaglia *et al.*, 1976; Chain *et al.*, 1977; Hennerici *et al.*, 1977; Nilsson, 1978; Shahrokhi *et al.*, 1978). None of these workers have succeeded in obtaining a 96% incidence of abnormal visual evoked potentials in patients with established or suspected multiple sclerosis as did Halliday *et al.* (1972, 1973b).

The present report deals with a comparison of results obtained by stimulation of visual and somatosensory pathways in a control group and in patients with established or suspected multiple sclerosis to examine whether the application of more tests can increase the diagnostic yield.

Subjects

The control group consisted of 36 subjects, aged 25-55 years, without history, signs or symptoms of involvement of the central or peripheral nervous system. The patient group comprised 50 individuals aged 21-64 years. They were classified in

three categories according to the criteria of McAlpine *et al.* (1972): (1) 28 definite cases of multiple sclerosis with signs and symptoms of at least two lesions localised to the CNS with a history of exacerbations and remissions; (2) 12 probable cases of multiple sclerosis with signs and symptoms of two or more lesions but without clear fluctuations; (3) 10 cases with possible multiple sclerosis due to a single characteristic lesion and a history of one or more partial remissions. Eight patients in this group had a slowly progressive spastic paraplegia of unknown origin.

Methods

VISUAL STIMULATION

The technique of pattern reversal stimulation was similar to that described by Halliday *et al.* (1972, 1973a, b). It consisted of back projection of a black and white checkerboard pattern on a semitranslucent screen with a diameter of 500 mm via a revolving mirror producing a lateral movement of one square width. The movement of the mirror took 3 ms and occurred each 500 ms. The subjects sat one metre in front of the screen, the stimulating field subtending 32° at the eye. The individual black or white square was 18×18 mm and had a luminance of 60 cd/m²±20% and 3100 cd/m²±10%, respectively. The background illumination was less than one lux. The subject was instructed to fixate a small cross in the centre of the screen. Pattern stimulation was presented to each eye in turn, the other eye being covered.

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SOMATOSENSORY STIMULATION

The median and common peroneal nerves were stimulated by a rectangular electric pulse (0.2 ms duration) from a double screened stimulator (DISA 14 Eol) via a surface electrode (DISA 13 k62) placed at the wrist and the head of the fibula respectively. The stimulus strength was one and a half times the motor threshold of the abductor pollicis brevis or peroneus longus muscles. Stimuli were presented to the nerves on each side in turn at 3 per second.

RECORDING

Visual evoked cortical potentials (VEP) were recorded via platinum needle electrodes placed at O1-OZ-O2 corresponding to the International 10-20 electrode system, using a reference electrode placed 50 mm in front of the vertex. Cortical potentials evoked by stimulation of the median and peroneal nerves (SEP) were recorded between needle electrodes placed over the somatosensory hand area and foot area respectively (Giblin, 1964) contralateral to the side of stimulation. The cortical activity was recorded via EMG amplifiers (DISA 15 Col) with a lower limiting frequency of 0.5 Hz and an upper of 1000 Hz (3 dB down) and was continuously displayed on an oscilloscope (DISA 15 Hol). The signals were transferred to a signal averager (Nicolet 1074) which was triggered by the pattern reversal or the nerve stimulator. The sampling time was 400 ms for visual and 200 ms for somatosensory evoked potentials. The average response to 128 pattern changes or electrical stimuli was recorded together with a calibration signal via an X-Y pen-plotter (HP 7044A), and then a further 128 stimuli were added to ensure reproducibility.

Results

NORMAL SUBJECTS

The pattern reversal VEP had the characteristic major positive component described by Halliday *et al.* (1972, 1973b) with a peak latency of 93 ms (SD 3.8 ms, $n=72$ eyes) independent of age (range 25-55 years). In half the subjects the major peak was preceded by a minor positive component with a peak latency of 51 ms (SD 3.6 ms, $n=36$ eyes) similar to that found by Asselman *et al.* (1975). The mean amplitude of the EP was $14 \mu\text{V}$ (range 6-34 μV). The change in latency of the major positive component as a function of the reversal time of the checkerboard pattern was studied in 19 subjects. Figure 1 shows recordings of the movement of the mirror at different speeds from 3 to 50 ms. Figure 2 shows the VEP recorded from one subject at different pattern reversal times. The

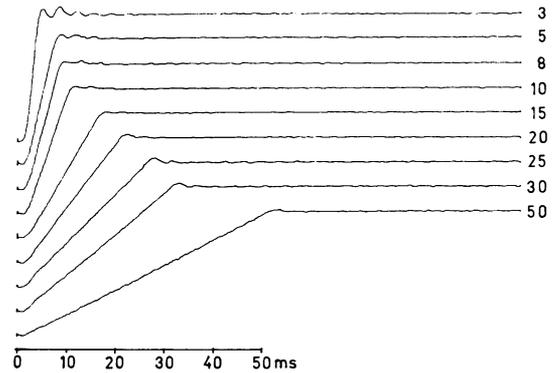


Fig. 1 Recordings of mirror movements used to produce pattern displacement of the checkerboard. The numbers to the right indicate the reversal time in ms.

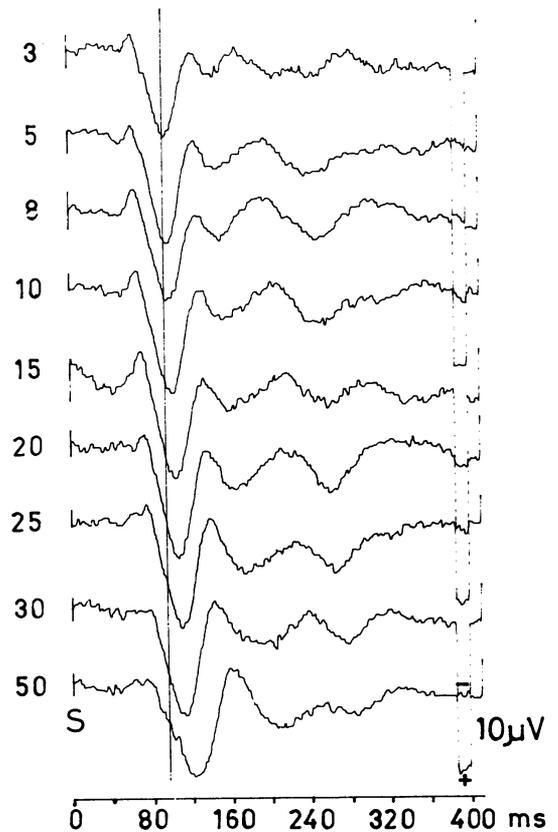


Fig. 2 Recordings from a normal subject of pattern reversal evoked potentials at different speeds of pattern displacement. The numbers to the left indicate the reversal time in ms. The vertical line indicates the latency of the major positive peak when the movement of the mirror took 3 ms.

latency of the VEP increased from 94 ms to 125 ms when the displacement of the mirror took 3 and 50 ms respectively. Figure 3 shows the relation between pattern reversal time and latency of VEP obtained from 19 subjects. The scatter of latencies was smallest when the movement of the mirror took 10 ms (SD 2.8 ms) and largest when it took 50 ms (SD 5.6 ms). The normal values of cortical potentials evoked by peripheral nerve stimulation are shown in Table 1. To accept a finding in the individual patient as abnormal we require a 99% probability that it does not occur in normal subjects of the same age; the upper 99% limits being 104 ms for VEP, 20 ms and 37 ms for SEP evoked by stimulating the median and the peroneal nerves respectively.

PATIENTS

Visual evoked potentials

There were 20 patients who had suffered an acute attack of retrobulbar neuritis of whom 16 were classified as definite cases of multiple sclerosis and four as probable. Three patients had had an affection of both eyes. A delayed or absent VEP was found in 94% of the definite cases of multiple

sclerosis who had had a history of retrobulbar neuritis compared to 85% in those who did not (Table 2). All patients with probable multiple sclerosis and a history of retrobulbar neuritis had abnormal responses compared to 26% of those without retrobulbar neuritis. Thus, all patients but one with a positive history of retrobulbar neuritis had abnormal VEP (96%). Of the 10 possible cases two had an abnormal VEP although they never had had clinical retrobulbar neuritis. Abnormal cortical responses were found on stimulation of both eyes in 23 patients with definite multiple sclerosis (82%) although only two had a history of bilateral visual disturbances (Table 3).

Figure 4 gives the distribution of the peak latencies of the major positive component of the VEP from affected and unaffected eyes. No response could be obtained from three affected and blind eyes. The absence of a response from one eye of a patient without retrobulbar neuritis was the result of previous traumatic retinal damage.

Somatosensory evoked potentials

In all patients but one the median nerve was

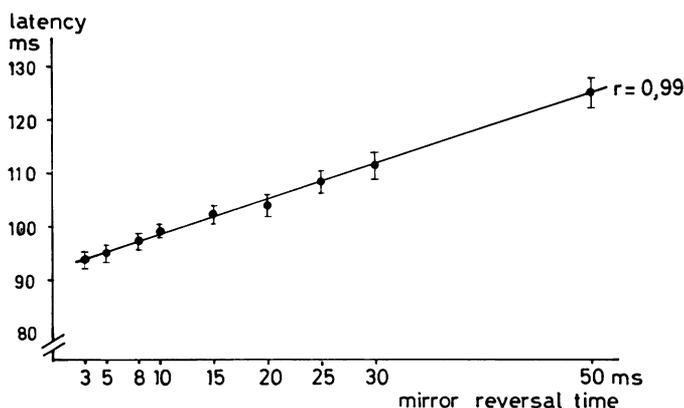


Fig. 3 Relation of pattern reversal time and latency of visual evoked potentials. Each dot represents the mean latency of the major positive component of the VEP from 19 normal subjects. The vertical bars indicate the standard error of the mean. r = correlation coefficient.

Table 1 Latencies (in ms) of components of cerebral response evoked in 17 healthy subjects by stimuli to left and right median and peroneal nerves

Nerve		Onset	1*	2†	3	4	5	Amplitude (μV)
Median	Mean	16	19	26	32	42	68	8
	SD	1.2	1.8	2.5	3.5	5.2	9.2	2
	Number	34	34	32	32	32	29	34
	Range	14-18	16-22	22-32	23-38	28-56	52-86	4-11
Peroneal	Mean	27	—	34	44	57	72	5
	SD	3.2	—	3.3	3.9	4.8	7.3	2.5
	Number	34	—	34	34	34	34	34
	Range	24-34	—	30-42	37-50	49-66	60-84	2-11

*Uneven numbers refer to negative going peaks.

†Even numbers to positive going peaks (Desmedt, 1971).

Table 2 Incidence (%) of abnormal visual (VEP) and somatosensory (SEP) evoked potentials in patients with established or suspected multiple sclerosis

Classification of MS	VEP				SEPM+P			
	abn/n†		-		abn/n‡		-	
	Number	%	Number	%	Number	%	Number	%
Definite (28)	17/18	94	33/38	85	34/42	88	24/57	42
Probable (12)	5/5	100	5/19	26	16/19	84	11/27	41
Possible (10)	0	0	2/20	10	7/10	70	6/30	20
Total (50)	22/23	96	40/77	52	60/71	85	41/114	36

M + P = median and peroneal nerves.

*Vibration or position sense or both.

†Number of eyes stimulated.

‡Number of hands and legs stimulated.

Table 3 Number of patients with established or suspected multiple sclerosis with delayed or absent visual (VEP) or somatosensory (SEP) evoked potentials

Classification of MS	EP	Abnormality		Total	
		Unilateral	Bilateral	Number	%
Definite (28)	VEP	4	23	27	96
	SEP _M *	9	9	18	64
	SEP _P	3	15	18	82
Probable (12)	VEP	4	3	7	58
	SEP _M	3	5	8	67
	SEP _P	3	6	9	75
Possible (10)	VEP	2	0	2	20
	SEP _M	3	1	4	40
	SEP _P	2	3	5	50

*Examined in 22 of the 28 patients, M = median nerve, P = peroneal nerve.

stimulated on both sides as was the peroneal nerve in 43 patients. Thus the analysis included 185 cortical responses. The results are shown in Table 2 in relation to whether or not vibration and posi-

tion sense or both were impaired. Clinically these senses were impaired or absent in 71 of 185 examined extremities (38%). Electrophysiologically, however, abnormalities were encountered in 101 (55%). Delayed or absent cortical responses were found in 88% of cases with definite multiple sclerosis in whom vibration or position sense or both were impaired compared to 42% in those with normal sensibility. Similar changes were found among cases classified as probable and possible multiple sclerosis.

Abnormalities were found bilaterally in half the patients when stimulating the median nerves and in three-quarters when stimulating the peroneal nerves, although only one-third and half of the patients had sensory disturbances corresponding to the upper and lower extremities respectively. Among the definite cases of multiple sclerosis a positive result was found more often when stimulating the peroneal than the median nerve (82% and 64% respectively). In the two other categories

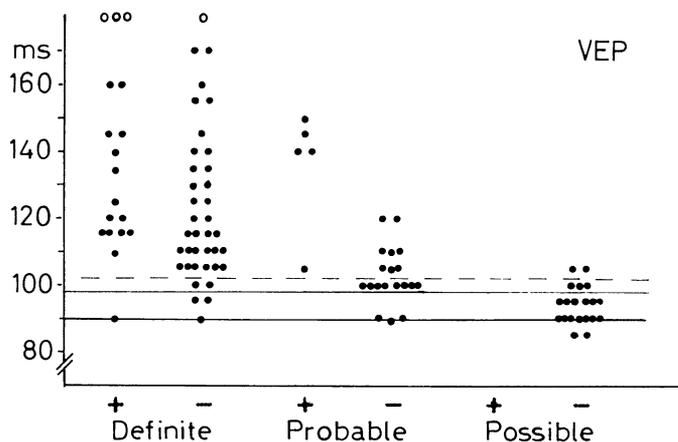


Fig. 4 Latencies of visual pattern reversal evoked potentials from both eyes in 50 patients with established or suspected multiple sclerosis. + = history of retrobulbar neuritis, - = no history of retrobulbar neuritis. Open circles indicate absence of cortical response. The thick horizontal line indicates the normal value, the thin and stippled lines the 95% and 99% upper confidence limits respectively.

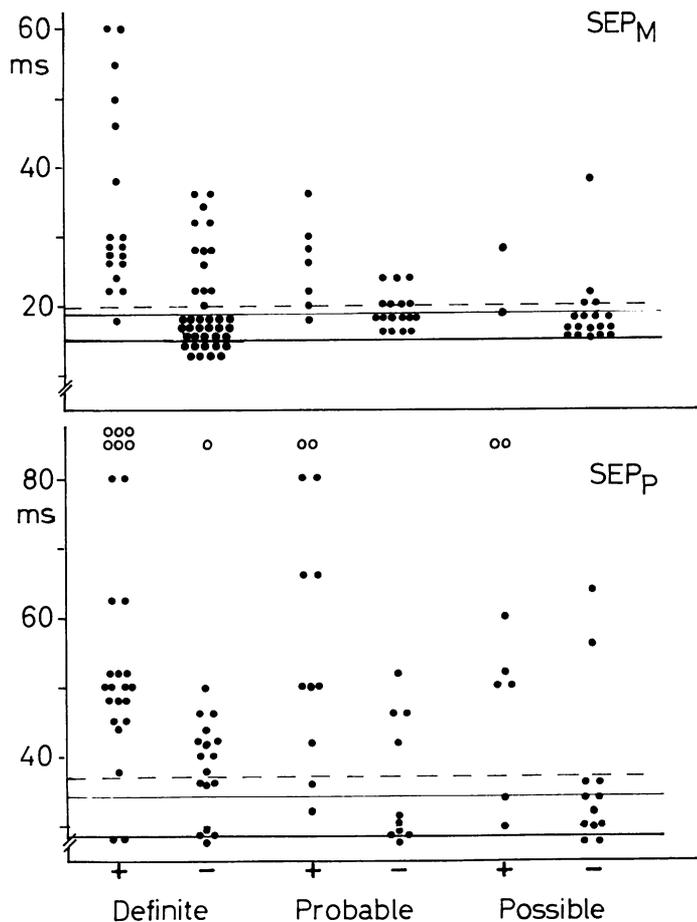


Fig. 5 Latencies of somatosensory evoked cortical potentials by stimulation of right and left median (SEP_M) and peroneal (SEP_P) nerves at the wrist and head of fibula respectively in 50 patients with established or suspected multiple sclerosis. +=impairment, -=no impairment of vibration or position sense or both. Open circles=absence of cortical responses. The horizontal thick lines indicate the normal mean value, the thin and stippled lines the 95% and 99% upper confidence limits respectively.

of patients the incidence of abnormal responses was about the same whether the median or the peroneal nerves were stimulated.

The individual values of latencies to the onset of the SEP are shown in Fig. 5. Some examples of SEPs are shown in Fig. 6. The most common abnormality was the absence of the first negative peak as described by Namerow (1968) and Tamuro and Kuroiwa (1972).

Both visual and somatosensory evoked potentials
The diagnostic yield when both techniques were applied is shown in Table 4. All patients with definite multiple sclerosis had abnormal cortical potentials to either visual or somatosensory stimulation. Among the probable cases of multiple sclerosis the diagnostic yield increased to 92% from 58% and 83% when only VEP and SEP were used respectively. Two of the 10 patients with possible multiple sclerosis had abnormal VEP and SEP,

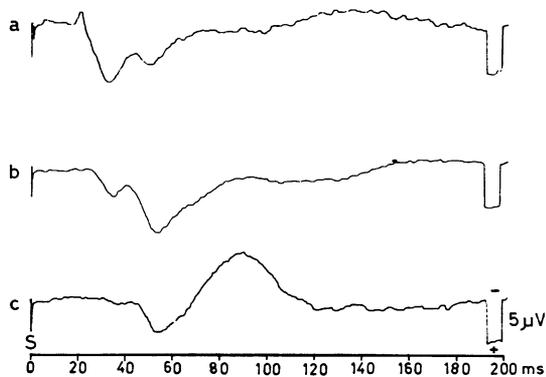


Fig. 6 Somatosensory cortical potentials evoked by stimulation of the median nerve at wrist. (a) Normal response from a 43 year old woman with probable multiple sclerosis. (b) Delayed response from a 42 year old woman with definite multiple sclerosis. (c) Delayed response from a 46 year old man with spastic paraplegia, grouped as possible multiple sclerosis. Note absence of N1 and the delay of P2 in (b) and (c).

Table 4 Number of patients with established or suspected multiple sclerosis with delayed or absent visual (VEP) and somatosensory (SEP) evoked potentials or both

Classification of MS	VEP		SEPM+P*		VEP+SEPM+P	
	Number	%	Number	%	Number	%
Definite (28)	27	96	19	86	28	100
Probable (12)	7	58	10	83	11	92
Possible (10)	2	20	5	50	5	50

M+P evoked by stimulating the median and the peroneal nerves respectively.

*Examined in 22 of the 28 patients with definite multiple sclerosis.

and a further three patients had abnormal SEP to both median and peroneal nerve stimulation.

Discussion

FINDINGS IN NORMAL SUBJECTS

The latency, amplitude, and shape of cortical potentials evoked by visual stimulation depend on a number of factors such as the intensity of the light, its wave length and character (patterned or unpatterned), the frequency of stimulation and, when patterned, the size of the pattern (Regan, 1972, 1975; Halliday *et al.*, 1973a). Moreover, with pattern reversal stimulation, the latency of the VEP depends on the speed of pattern displacement. Using the method of Halliday *et al.* (1972, 1973b) we found that the latency increased linearly with increasing pattern reversal time from 3 to 50 ms; the increase in latency being 0.6 ms per millisecond increase in reversal time. Thus, the differences in mean latency of pattern reversal VEP between different studies can be accounted for by variations in technique. It is, therefore, necessary to use a standardised method and to establish normal values for comparison with findings in patients.

As to the mean peak latencies of somatosensory evoked potentials there is better agreement between different studies. The latency is not affected by variation of stimulus intensity from a level just above sensory threshold to the maximal level tolerated, whereas the amplitude, especially of the early components of the SEP, increases with increasing stimulus intensity (Hume and Cant, 1978).

FINDINGS IN PATIENTS

Among 50 patients with established or suspected multiple sclerosis we found, in agreement with Lowitzsch *et al.* (1976), delayed or absent cortical responses to pattern reversal stimulation in 72% in contrast to the 96% found by Halliday *et al.* (1972, 1973b). This very high overall proportion of

abnormalities seems not to have been reproduced so far. In different reports the incidence of abnormalities varies from 50% to 75% (Asselman *et al.*, 1975; Mastaglia *et al.*, 1976; Hennerici *et al.*, 1977; Matthews *et al.*, 1977; Shahrokhi *et al.*, 1978; Nilsson, 1978).

In patients with multiple sclerosis established on other grounds we found, as Halliday *et al.* (1972, 1973b), abnormal VEP in 97% compared to 79–88% by others (Asselman *et al.*, 1975; Lowitzsch *et al.*, 1976; Hennerici *et al.*, 1977; Matthews *et al.*, 1977; Shahrokhi *et al.*, 1978; Nilsson, 1978). A similar high proportion of abnormal responses to somatosensory stimulation was found in the present study, and when combining the results of these tests with those of pattern reversal stimulation abnormalities were found in all the definite cases of multiple sclerosis.

It is, however, of more interest that among patients classified as probable cases, in whom about half had delayed response to visual stimulation, the diagnostic yield increased to 92% when combined with the results of somatosensory stimulation. That Mastaglia *et al.* (1977) obtained an increase in the proportion of abnormalities from 54 to 64% can only be explained by the fact that they recorded cortical potentials to stimulation of the median nerve alone whereas we in addition recorded cortical potentials evoked by stimulation of the peroneal nerve.

The incidence of delayed VEP among patients with possible multiple sclerosis varies considerably between different reports. Halliday *et al.* (1973b) found abnormal VEP in 11 of 13 such cases whereas Asselman *et al.* (1975) did so in only three of 14 patients. Other reports indicate incidence of abnormality from 33–70% (Lowitzsch *et al.*, 1976; Chain *et al.*, 1977; Matthews *et al.*, 1977). Among our 10 cases of possible multiple sclerosis, two had delayed VEP and three had delayed SEP—that is, in half the cases the electrophysiological investigation supported the clinical suspicion.

The patients with chronic progressive spastic paraplegia represent a special problem. They are usually classified as possible cases of multiple sclerosis when other causes have been excluded. A clinical follow-up of such patients has shown that one-third develop further signs and symptoms suggestive of multiple sclerosis (Marshall, 1955; Hübbe and Mouritzen, 1973). Similarly, at necropsy, Marshall (1955) found that 12 of 35 cases had multiple sclerosis of which half were diagnosed before death, while the remaining had either medullary compression, vascular or osseous abnormalities causing the paraplegia. In five of our eight cases of chronic paraplegia we found delayed

SEP, but no abnormality of VEP. However, Halliday *et al.* (1973b) found delayed VEP in five of 13 patients with spastic paraplegia, and Matthews *et al.* (1977) found abnormal VEP in four of their nine patients. The incidence of abnormal VEP is lower in patients with chronic progressive paraplegia than in definite and probable cases of multiple sclerosis but the proportion of abnormality is similar to what could be expected from necropsy findings. It may, therefore, be that the paraplegic patients with normal evoked potentials do not have multiple sclerosis.

The value of EP methods in the early diagnosis of multiple sclerosis—when there has been only one transient episode of neurological symptoms outside the visual system—is not evident from this nor from other studies. Halliday *et al.* (1973b) found normal VEP in six patients with a single attack suggesting brainstem involvement, whereas Asselman *et al.* (1975) described delayed VEP in six of 13 patients with similar symptoms. Matthews *et al.* (1977) examined 39 patients with a single acute episode resembling multiple sclerosis and found delayed VEP in only two. However, a follow-up of these two patients confirmed the clinical suspicion as they entered into one of the diagnostic categories of multiple sclerosis. The fate of the remaining patients is unknown.

It has been shown that recording of brainstem evoked responses by auditory stimulation can be helpful in the diagnosis of multiple sclerosis (Robinson and Rudge, 1977; Stockard *et al.*, 1977), but it is not known whether this method leads to positive results when the other evoked potential techniques fail to reveal abnormalities.

It is promising to know that a refinement of pattern reversal stimulation can increase the diagnostic yield especially among the cases of possible multiple sclerosis. Thus, Hennerici *et al.* (1977) found that using a small white square subtending 45' instead of the conventional 20° increased the incidence of abnormal VEP from 43% to 78%. Similar results were obtained by Nilsson (1978) using light-emitting diodes of red colour to produce a pattern reversal.

The somatosensory cortical evoked potential has not been widely accepted as a tool in the diagnosis of multiple sclerosis. Namerow (1968) recorded SEP from 58 hands of 40 patients with definite multiple sclerosis and found abnormal responses from 43 hands (74%). In smaller series of cases of definite multiple sclerosis studied by Tamuro and Kuroiwa (1972, n=16) and Mastaglia *et al.* (1977, n=14) there were abnormal responses in 50%. We found a much higher incidence of abnormality in patients with established multiple sclerosis (86%) when

combining the results obtained by stimulating the median and peroneal nerves—that is, nearly the same proportion of abnormality as when using VEP. Abnormal SEPs were found more frequently than abnormal VEPs in our cases of probable and possible multiple sclerosis. Whether this is merely an incidental finding awaits further confirmation.

Our findings that patients with impaired vibration and position sense more often have delayed SEP than those with intact sensation are in agreement with previous reports (Halliday and Wakefield, 1963; Giblin, 1964; Larsson *et al.*, 1966; Namerow, 1968), and thus support the suggestion that the posterior columns are the main pathway for the SEP (Larsson *et al.*, 1966).

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