Visual fatigue and visual evoked potentials in multiple sclerosis, glaucoma, ocular hypertension and Parkinson's disease

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SUMMARY Visual evoked potential (VEP) abnormality is widely used as an objective indication of visual pathophysiology in the diagnosis of multiple sclerosis. One major limitation of this test is that VEP abnormality is not specific to multiple sclerosis. In an attempt to explore ways of making the VEP test more specific, changes were measured in VEPs caused by superimposing upon the VEP stimulus either a flicker or a moving pattern. The rationale was to test for visual fatigueability, since it is known that some demyelinated axons fatigue rapidly. Of 10 patients with multiple sclerosis, 90% showed VEP fatigue, while none fatigued in the groups of 10 patients with glaucoma and 10 with Parkinson's disease. Fatigue is, however, not completely specific for multiple sclerosis, since three of 10 patients with ocular hypertension showed VEP fatigue.

During the decade that has passed since the report of Halliday *et al*¹ that pattern visual evoked potentials (VEPs) are delayed in patients with multiple sclerosis, pattern VEP recording has been widely adopted as an aid to the diagnosis of multiple sclerosis. The most useful features of the VEP technique are its objectivity and the empirical finding that VEPs can be abnormal even when there is no clinical evidence of visual involvement. One major limitation of the VEP technique remains, however. As pointed out by Halliday *et al*^{1,2} abnormal pattern VEPs are not specific to multiple sclerosis: many different diseases have been found to cause delayed or otherwise abnormal VEPs.^{2,3} In this note, we describe preliminary experiments whose aim was to improve the specificity of VEP tests.

Our rationale was as follows. Animal studies have shown that some demyelinated axons fatigue rapidly and are unable to conduct at high firing rates.⁴⁻⁷ Furthermore, visual fatigue can be experimentally induced in patients with multiple sclerosis,⁸ and is sometimes reported as a clinical symptom. We reasoned that, if the conventional pattern VEP test could be combined with a test for visual fatigue, the new test might be more specific for multiple sclerosis than the conventional VEP delay test.

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Methods

Apparatus and procedure

Pattern stimulation was conventional. A TV stimulator (Nicolet model 1005) was viewed monocularly from 134 cm. The unstimulated eye was occluded. The checkered pattern subtended 9.7° (horizontal) $\times$ 7.6° , and the side length of the black and white checks was 45 min arc. The luminance of the bright squares was 2.7 ft lamberts (9.3 d/m^2), and the contrast of the checkerboard pattern alone was close to 100%. Subjects fixated a cross at the centre of the field. The checkerboard pattern reversed 1.9 times per second. Each reversal triggered an averaging computer whose sweep time was 300 ms. A total of 200 sweeps was summed for each trace. The amplifier bandpass was 1 to 30 Hz.

In the first experiment the checkerboard field was superimposed on a bright, rectangular area subtending 10.8° (horizontal) $\times$ 8.7° that reduced the pattern contrast to 60%. The superimposed light was generated by a raster scan on a Hewlett-Packard CRT (model 1321A). First, a monocular pattern VEP was recorded with the superimposed light steady. Then a VEP was recorded with a superimposed light flickering, but of the same mean luminance. The flicker waveform was white noise, low-pass filtered with a corner frequency of 0.9 Hz. The irregularly-flickering light contained clearly-visible rapid flicker components of about 5 Hz. Note that the only difference between these two stimulus conditions was that the superimposed homogeneously-illuminated area was steady in one case and flickering in the other. Then the two VEP recordings were repeated. Finally, the four recordings were carried out for the subject's other eye.

In the second experiment, the fatiguing stimulus was a

Table 1 Clinical summaries

Patient	Age (yr)	Sex	Visual acuity		Diagnosis	Symptoms
			OD	OS		
1	36	M	6/6	6/4.5	MS	Uhtoff's, RBN OD Aug 82, weakness & numbness lower limbs
2	41	F	6/6	6/6	Nil	Numbness legs (variable), vague double vision
3	36	F	6/7.5	6/7.5	MS	Transverse myelitis, spasticity lower limbs, incoordination hands, visual blurring 1 yr.
4	52	F	6/7.5	6/7.5	MS	Spastic paralysis legs, decreased sensation 1. arm, truncal incoordination
5	37	F	6/9	6/7.5	MS	Weakness both legs, numb feet, RBN OS Feb 82, RBN OD Sept 82
6	33	M	6/6	6/6	MS	T. myelitis, RBN OD occurred and resolved 1976, RBN OS Sept 82
7	30	M	6/7.5	6/4.5	Nil	RBN OD 16 Nov 82
8	42	F	6/7.5	6/6	MS	Numbness both forearms 1962, RBN OD 1963, weakness legs 1970, blurring of VA with effort
9	48	F	6/6	6/7.5	MS	Spastic paralysis both legs, bladder dysfunction, diplopia 1981
10	39	M	6/9	6/7.5	MS	RBN OD 1965 & 1972, spastic gait 1962, numbness & weakness 1. leg 1967, bladder spastic

MS = multiple sclerosis
RBN = retrobulbar neuritis

moving pattern, rather than a flickering, homogeneous rectangular area. First, as in Experiment 1, a monocular pattern VEP was recorded with the superimposed rectangle of homogeneous light steady. Then, by using a special-purpose electronic circuit, the superimposed rectangle of light was transformed without any change in mean luminance from a homogeneously-illuminated area to an area of checks subtending 50 min arc side length. This area of checks was oscillated from side to side horizontally by a white noise waveform that was low-pass filtered with a corner frequency of 0.1 Hz (RMS amplitude about 60 min arc), and at the same time oscillated vertically with a different noise waveform of similar bandpass and amplitude. Consequently, the superimposed pattern was in two-dimensional, pseudo-random motion. A pattern VEP was recorded under these conditions. Then the two VEPs were repeated. Finally, all four VEP recordings were carried out for the subject's other eye.

Because the averager was triggered by the Nicolet pattern stimulator, neither the superimposed flicker nor the superimposed moving pattern was synchronised to the averager. Therefore, neither the flicker nor the superimposed moving pattern contributed directly to the averaged VEP. Rather, we recorded the effect of the superimposed fields upon the pattern VEP due to the Nicolet stimulator.

Recording time for the flicker fatigue experiments was about 20 min, and similarly for the pattern fatigue experiment. All recordings were made between an inion electrode and an electrode 1/4 of the inion-nasion distance anterior along the midline. A midfrontal electrode was grounded.

Patients and control subjects

The two experiments were carried out for 10 control subjects and 10 patients with demyelinating disease. Similar measurements were made in 10 patients with ocular hypertension, 10 patients with Parkinson's disease and 10 patients with glaucoma. Informed consent was obtained after the procedures had been fully explained. Table 1 gives clinical summaries for the 10 patients with demyelinating disease. The mean age was 36 years (range

26-60) for control subjects, 39 years (range 30-52) for patients with demyelinating disease, 59 years (range 41-73) for glaucoma, 56 years (range 45-66) for ocular hypertension and 60 years (range 41-79) for Parkinson's disease. Corrected visual acuities were 6/6 or better in all control eyes.

Results

EFFECTS OF SUPERIMPOSED FLICKER UPON PATTERN VEP AMPLITUDE IN PATIENTS WITH DEMYELINATING DISEASE

Figure 1A illustrates that superimposed flicker had a slight tendency to attenuate VEP amplitude in most control subjects. Two recordings are shown for each stimulus condition as an indication of reproducibility. Table 2 gives numerical control data for 20 eyes with normal limits. Figure 2 compares the effects of flicker upon pattern VEP amplitude for the control group's eyes, for eyes which had a history of retrobulbar neuritis or showed optic atrophy, and for the supposedly unaffected eyes in patients. Figure 2 shows that flicker had comparatively little effect on VEP amplitude in control subjects. The arrows on the abscissa of fig 2 mark our upper normal limits, 2.5 SD from the control mean. About 99% of controls will fall inside these limits. Figure 2 shows that, of 16 eyes with a history of retrobulbar neuritis or with pale discs, nine fell outside normal limits on the flicker fatigue test. Of 10 patients tested, seven had abnormal flicker fatigue in one or both eyes. Of 10 patients with delayed VEPs in the conventional large-check test, seven were abnormal on flicker fatigue. Two patients gave normal VEPs in the conventional large check test, but these VEPs were abnormal on the flicker fatigue test.

Table 2 Control data for VEP fatigue

Test	No. of eyes	Mean	SD	Upper and lower normal limits
Flicker fatigue	20	VEP Amplitude without Fatiguing Stimulus		1.5; 1/1.6
		VEP Amplitude with Fatiguing Stimulus	0.2	
		1.05		
Moving pattern fatigue	20	VEP Amplitude with Fatiguing Stimulus		1.5; 1/1.6
		VEP Amplitude without Fatiguing Stimulus		
		1.1	0.21

Fig 1 Changes in VEP amplitude caused by superimposing either flicker or moving pattern on the visual stimulus. Two repeats of each recording are shown for a typical control subject. A—The upper traces are VEPs elicited by a checkerboard pattern stimulus that was superimposed on a steadily-illuminated area. The lower traces show that flickering the illuminated area slightly reduced VEP amplitude. B—VEPs elicited by a checkerboard pattern stimulus that was superimposed on a moving pattern (lower traces). The moving pattern slightly enhanced VEP amplitude.

EFFECTS OF SUPERIMPOSED MOVING CHECKS UPON PATTERN VEP AMPLITUDE IN PATIENTS WITH DEMYELINATING DISEASE

The superimposed moving pattern had an overall tendency to slightly enhance VEP amplitude in control subjects (fig 3). The arrows on fig 3 mark the normal limits, 2.5 SD from the control mean. Figure 3 shows that, of eyes with a history of retrobulbar neuritis or with pale discs, six fell outside normal limits. In addition, one "unaffected" eye fell outside the control range. Of 10 patients tested, seven fell outside control limits in one or both eyes. Of 10 patients with delayed VEPs in the conventional large-check test, seven were abnormal on pattern fatigue.

LATENCY EFFECTS IN PATIENTS WITH DEMYELINATING DISEASE

Flicker or moving pattern caused latency to become abnormal in three patients.

VEPs IN PATIENTS WITH OCULAR HYPERTENSION, PARKINSON'S DISEASE AND GLAUCOMA

Of 10 patients with glaucoma, four had delayed VEPs, and of 10 patients with Parkinson's disease, two had delayed VEPs. None showed fatigue. Of 10 patients with ocular hypertension, four had delayed VEPs. Two of these four patients showed fatigue to flicker. One patient with undelayed VEPs showed VEP fatigue to flicker. It is not altogether surprising that four patients with ocular hypertension had delayed VEPs even though clinical perimetry (Goldmann and Octopus) detected no neuro-ophthalmological involvement, since it is known that a substantial proportion of patients with ocular hypertension with no clinical field defects have abnormal contrast sensitivity in the peripheral visual field.⁹⁻¹¹

PATTERN FATIGUE VERSUS FLICKER FATIGUE

Our reason for comparing the fatiguing effects of a moving pattern with the fatiguing effects of a flickering homogeneous field was as follows. We supposed that the irregularly-moving pattern would increase the mean firing frequencies of neurons sensitive to spatial pattern, thus tending to fatigue them, whereas flicker would increase the mean firing frequencies of neurons sensitive to changes in overall luminance. Therefore, we argued, if a patient's VEPs showed abnormal fatigue to moving pattern but not to flicker, then this would indicate a lesion located at or central to the site of the most peripheral pattern-sensitive neurons. Conversely, if fatigue occurred for flicker but not for moving pattern, then this would suggest that the responsible lesions did not involve pattern-sensitive neurons. We found that the VEPs of three patients with multiple sclerosis showed abnormal fatigue for both flicker and pattern, and four multiple sclerosis patients fatigued for flicker but not for pattern. One patient showed marked differences to pattern only.

Discussion

Evoked potential delay is not specific to any single

Fig 2 Changes in VEP amplitude caused by superimposing flicker on the visual stimulus. Each dot represents one eye. Increased amplitudes are plotted to the right of centre, and decreased amplitudes to the left. Numbers on the ordinates are ratios between VEP amplitude with and without flicker. The arrows mark normal limits for control subjects (mean plus 2.5 SD). Several patients' eyes fatigued abnormally, falling outside the normal range.

disease or group of diseases; it is known that VEPs are delayed, not only in multiple sclerosis, but also in some patients with glaucoma,¹² amblyopia,¹³ spinocerebellar degeneration,¹⁴ compressive lesions,¹⁵ hereditary spastic paraplegia¹⁶⁻¹⁸ and Parkinson's disease.¹⁹

The aim of this preliminary study was to explore a possible means of modifying the standard VEP delay test so as to render it more specific for multiple sclerosis. We have attempted to exploit the visual fatigueability associated with demyelination.

Our chief finding is that, of 10 multiple sclerosis patients with delayed VEPs, seven showed abnormal attenuation when the pattern-reversal stimulus was accompanied by flicker and seven showed abnormal attenuation when moving checks were superimposed on the pattern stimulus. In total 9/10 were abnormal on one or other fatigue test. One patient showed abnormal latency changes only. The one patient who showed no fatigue was the only one

who had no history of clinical visual signs or symptoms.

We conclude that not all VEP delays are the same. Fatigue tests can distinguish between disease that produce otherwise-similar VEP delays; none of 20 patients with glaucoma and Parkinson's disease showed fatigue, compared with the 90% of multiple sclerosis patients whose VEPs fatigued. We suggest that the standard VEP diagnostic test could be made more specific for multiple sclerosis by adding a fatigue measurement. Complete specificity is not achieved, however, because fatigue tests do not distinguish between multiple sclerosis and ocular hypertension. Perhaps the fatigue tests reveal the presence of neurons in the visual pathway that are functioning with a reduced safety factor. Presumably, functional integrity would be reduced by partial demyelination in multiple sclerosis and by persistently elevated interocular pressure in ocular hypertension while, in our glaucoma patients,

Fig 3 Changes in VEP amplitude caused by superimposing moving pattern on the visual stimulus. Each dot represents one eye. Increased amplitudes are plotted to the right of centre, and decreased amplitudes to the left. Numbers on the ordinates are ratios between VEP amplitude with and without flicker. The arrows mark normal limits for control subjects (mean plus 2.5 SD). Several patients' eyes fatigued abnormally, falling outside the normal range.

neurons were either unaffected or completely non-functional.

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