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Clinical Section

MECHANISMS OF EPILEPTOGENESIS IN PHOTOSENSITIVE EPILEPSY IMPLIED BY THE EFFECTS OF MOVING PATTERNS

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Summary The triggering of epileptiform EEG discharges by pattern is thought to depend on the intensity of excitation within the visual cortex. The present study investigates the role of the synchronisation of neuronal activity by the stimulus. In 10 pattern-sensitive subjects the effects of the following patterns have been compared: (1) static gratings, (2) gratings oscillating in a direction orthogonal to the lines (which should synchronise activity in direction-sensitive cortical units), and (3) gratings drifting at the same angular velocity (which should produce little or no synchronisation, because the contours enter and leave the overlapping receptive fields of individual neurones asynchronously). The oscillating gratings were most, and the drifting least, epileptogenic. In 2 further subjects oscillating and phase-reversing patterns were more epileptogenic than drifting gratings. Although open to alternative explanations, the findings conform with predictions from the hypothesis that synchronisation of individual cortical neurones by the stimulus contributes to epileptogenesis in photosensitive subjects.

Keywords: *photosensitive epilepsy – pattern stimulation – synchronisation*

Intermittent photic stimulation (IPS) can produce synchronous activity of visual cortical neurones, but it is uncertain what role such synchronisation might play in epileptogenesis. At frequencies between 15 and 18 flashes/sec which are the most epileptogenic in photosensitive humans (Jeavons and Harding 1975), neurones in the visual cortex of the cat do not exhibit one-to-one following of the flicker stimulus (Kuhnt and Creutzfeldt 1971).

We have previously reported several studies of patients with photosensitive epilepsy in whom epileptiform EEG discharges were consistently elicited by the viewing of static grating patterns (Wilkins et al. 1980). These studies implicated a trigger mechanism involving binocularly innervated neurones with complex properties. We also showed that the probability of eliciting a discharge was dependent on those stimulus characteristics that determine the intensity of activation of individual neurones in the visual cortex (linearity, spatial frequency, contrast, etc.) and by the area of cortex to which the pattern projected within either hemisphere. We have found that oscillation of a grating pattern greatly enhances its epileptogenic properties; moreover the optimum oscillation frequency is in the range of 15–20 Hz (Binnie et al. 1979), a frequency range at which intermittent diffuse light is also maximally epileptogenic. It is conceivable that oscillating patterns and intermittent light contribute to epileptogenesis by virtue of the synchronisation of the excitation they induce.

The following study tested the hypothesis that synchronisation of neuronal activity by a visual stimulus can indeed contribute to epileptogenesis. Patients with photosensitive epilepsy took part. The patients had undoubtedly epileptic seizures and exhibited a classical photoconvulsive response (Bickford et al. 1952), although the seizures were not necessarily elicited only by environmental visual stimulation. (For a discussion of the relationship between photosensitivity and photosensitive epilepsy see Jeavons and Harding 1975; Newmark and Penry 1979; Wilkins et al. 1980.)

Black and white grating patterns (with square-wave luminance profile) were presented under 3 different conditions.

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(1) Oscillating pattern

The grating oscillated with a triangular wave form, that is the velocity of contours was constant through the range of movement and then changed abruptly in sign. The movement was in a direction orthogonal to the line orientation and had an amplitude of one-half spatial cycle. Such a stimulus might be expected to produce synchronous activities in at least 3 populations of direction-sensitive cortical units: those responding to movement in one or the other direction should fire synchronously but with a phase difference of about 180°; those sensitive to movement in both directions should fire more or less continuously or, possibly, in bursts at twice the frequency of oscillation.

(2) Drifting pattern

When a grating moves through the visual field in one direction with constant velocity, the contours enter and leave the overlapping receptive fields of individual cortical neurones asynchronously. A drifting pattern might therefore be expected to excite neurones without contributing to the temporal organization of cortical neuronal activity.

(3) Static pattern

The retinal image of a static grating is continuously in motion due to the various movements of the eye during fixation. Following the arguments in the preceding paragraphs this movement might produce some degree of synchronisation of neuronal activity, although less than that induced by a pattern oscillating rhythmically, and more than that for a pattern drifting continuously in one direction.

The hypothesis that the synchronisation of visually induced cortical activity contributes to epileptogenesis therefore leads to the prediction that oscillating patterns should be more epileptogenic than drifting, and that the effects of static patterns should fall between these extremes. The studies to be reported confirm this prediction.

Experiment I

Methods

Subjects. The experiments were performed with the help of 10 consenting patients with epilepsy who were pattern-sensitive and whose other main clinical characteristics are summarized in Table I.

TABLE I

Experiment I: characteristics of patients.

Patient	Age (years)	Sex	Type of epilepsy	Medication (mg daily)
1	13	M	Primary generalised	VPA 600
2	23	M	Partial	Nil
3	23	M	Primary generalised	VPA 1500
4	19	F	Primary generalised	VPA 1500 ESM 750
5	18	F	Partial	VPA 1800
6	26	F	Partial	CBZ 1400 PHT 275
7	14	F	Uncertain	Nil
8	13	F	Secondary generalised	CBZ 300
9	13	M	Secondary generalised	Nil
10	19	F	Primary generalised	Nil

Apparatus. An important consideration in the design of the apparatus for visual stimulation was the avoidance of optokinetic nystagmus by the moving patterns. This was achieved by displacing the oscillating or drifting gratings symmetrically in opposite directions on either side of a central fixation point. Monocular monitoring of eye movements in two patients and one control subject using a sensitive infra-red limbus tracker (resolution about 5 min of arc; Findlay 1974), and binocular monitoring in 4 control subjects using diffuse infra-red scleral reflection (resolution about 5 min of arc; A.C.S. Applied Research Developments Ltd.) both failed to reveal any evidence of optokinetic nystagmus.

A high resolution (1024 lines) high frequency (60 Hz fullframe) TV monitor (Moniterm VR 1000, phosphor type WD, persistence < 10 msec) was used to present static, drifting or oscillating patterns as described above, with a square-wave luminance profile, and a spatial frequency of 2 c/degree at a viewing distance of 0.3 m. The angular subtense was 30° (horizontal) by 25° (vertical). The grating was generated by driving the Z-modulation of the cathode ray tube with a square wave oscillator synchronised to the TV raster. Move-

ment was controlled by signals from a Kontron Psi 80 microcomputer applied to the time base scan. The contrast was 0.81 and the mean luminance 93 cd/m^2. During the experiments the ambient lighting was of the order of 50 lux, which was sufficient to observe the patient to determine whether possible clinical ictal events accompanied the discharges. None was in fact observed. The frequencies of oscillation for the triangular profile of pattern movement were 5, 10, 15 and 20 Hz with an amplitude of one-half cycle (15 min of arc). The displacement velocity in each direction was therefore constant, corresponding to values of 2.5, 5, 7.5 and 10°/sec. The drifting patterns were presented at the same angular velocities.

Procedure. Prior to each experimental session, sensitivity to IPS and static patterns was confirmed by the methods which we have reported elsewhere (Wilkins et al. 1979). The experimental stimuli were then presented in an order randomised both for test condition (oscillating, drifting or static pattern) and for velocity or frequency. As previous studies had indicated frequencies close to 15 Hz to be optimal for eliciting discharges with oscillating pattern, particular attention was directed to this frequency and to the corresponding (7.5°/sec) drift velocity. Each stimulus was presented under constant conditions for a maximum of 10 sec, but was terminated immediately if a clear discharge of spikes or spike-wave activity was elicited. The records were subsequently reassessed by an observer who did not know in what order the various stimuli had been presented.

Results

The findings are summarised in Table II. It will be seen that in all subjects the patterns oscillating at 10–20 Hz were most, and the drifting patterns least epileptogenic, the static patterns giving intermediate results. Indeed, a discharge was elicited with a drifting pattern on only 4 occasions. There was no obvious association between eye movements and the occurrence of a discharge.

Experiment II

In experiment II the patterns previously used were compared with phase-reversing gratings to see whether the difference between drifting and oscillating patterns depended on a change in the direction of pattern movement. Each change of phase of a phase-reversing grating might be expected to result in an excitation of visual neurones. The excitation should therefore show some degree of temporal organisation and in this respect resemble the excitation from vibrating gratings. However, the populations of cells stimulated should differ from those stimulated by vibrating gratings, at least in so far as the populations sensitive to one

TABLE II

Experiment I: probability of epileptiform activity in response to oscillating, static and drifting patterns.

Patient	Oscillating pattern				Static pattern	Drifting pattern (degrees/sec)			
	Frequency (Hz)								
	5	10	15	20		2.5	5	7.5	10
1	0	1	1	1	0.5	0	0	0	0
2	0	1	1	0	1	0	0	0	0
3	0	0	0.8	0	0.4	0	0	0	0
4	0	0	1	0	0.25	0	0	0	0
5	0	0	1	1	0	0	0	0	0
6	–	0	1	1	0.5	0	0	0	0
7	0	1	1	1	0.8	0	0	0.17	0.33
8	0	0	1	1	0.22	0	0	0.1	0
9	0	0	1	0	0.33	0	0	0.1	0
10	0	0	1	0	0	0	0	0	0
Total	0	0.4	0.97	0.5	0.38	0	0	0.04	0.04

direction of movement should not be selectively excited. Nevertheless, if temporal organisation contributes to epileptogenesis then phase-reversing gratings should be more epileptogenic than those that drift (as has previously been argued, drifting gratings should not produce excitation with any gross temporal organisation).

The apparatus described in experiment I used a cathode ray tube display with a refresh rate of 60 Hz. There have been recent reports that in the visual system of the cat there exist neurones that fire synchronously with intermittent light at frequencies as high as 120 Hz (Eysel and Burandt 1984). It is therefore possible that the difference between drifting and oscillating patterns observed in experiment I might have been more dramatic had the display not been intermittently illuminated. For this reason a different apparatus was constructed for use in experiment II, which generated drifting, oscillating and phase-reversing gratings with a constant illumination.

Methods

Subjects. Two male patient volunteers (the first aged 18 and the second aged 25) were tested. Both were receiving sodium valproate for relief of primary generalised epilepsy, and both were sensitive to diffuse intermittent photic stimulation. They were also sensitive to stationary patterns of stripes with a spatial frequency of 2 c/degree, subtending 20°. These patterns had been presented as part of the clinical assessment of the patients. In comparison with these patterns, the patterns used in the present experiment had a lower mean luminance and under these conditions the patients were not sensitive when the patterns were stationary. Stationary patterns were not included amongst the experimental stimuli because of time constraints.

Apparatus. The apparatus consisted of patterns mounted on a cylinder that was rotated at a variety of speeds by a servo-controlled motor. The cylinder was painted white, and by means of a lathe, a spiral of black plastic tape was wound over part of the outer surface. Another spiral with opposite sense was wound onto a neighbouring part of the cylinder so that when the latter was rotated, the effect was to produce two patterns of stripes each drifting towards the junction of the two patterns. Over another part of the surface of the cylinder two similar spirals, each with opposite sense, were wound, one on top of the other. These were then cut along two diametrically opposed axes parallel with the axle of the cylinder at the points at which the spirals overlapped, and half of each spiral then removed. With each rotation, the stripes moved first in one direction by one-half of a spatial cycle (or one stripe width) and then in the opposite direction by an equivalent amount. On a third part of the cylinder was mounted a printed grating with stripes orthogonal to the horizontal axle of the cylinder. The pattern was cut along two diametrically opposed axes parallel with the axle and the stripes of one-half of the pattern offset in opposite phase, so that with each rotation of the cylinder the phase of the pattern reversed twice.

The patterns were thus all vertical gratings which moved in a horizontal direction. They had a square-wave luminance profile, a Michelson contrast of 0.7 and at a viewing distance of 0.5 m the drifting and oscillating patterns had a spatial frequency of 2.8 c/degree. The phase-reversing pattern had a similar spatial frequency but at a viewing distance of 0.4 m. The 3 patterns were viewed through an outer stationary cylinder via separate rectangular windows (measuring 750 mm wide by 950 mm high), each of which was covered by a grey shutter with the same mean reflectance. Along the vertical midline of each window a grey strip 5 mm wide divided the left and right visual hemifields and in its centre a red 1 mm dot was provided for fixation.

Care was taken to ensure that the mounting of the patterns on the cylinder was not eccentric. For the drifting and oscillating patterns, which were applied by lathe, there was no discernible eccentricity. For the phase-reversing pattern, deviations of the lines with the rotation of the cylinder were difficult to avoid. These deviations, which were of the order of 0.2 mm, were very small in relation to the change in phase.

Procedure. The patterns were viewed under tungsten filament illumination and had a mean luminance of 34 cd/m^2. A trial began when the shutter was lifted and the volunteer was instructed to fixate the red dot. If epileptiform EEG activity occurred the shutter was dropped immediately,

TABLE III

Experiment II: probability of epileptiform activity in response to oscillating, phase-reversing and drifting patterns.

Oscillating patterns						
Frequency (Hz)	2.5	5	10	20	30	40
Velocity (deg/sec)	0.89	1.78	3.57	7.14	10.7	14.3
Patient 1	0	0	1.0	0.5	0.5	0
Patient 2	0	0	0	0.5	0.5	0
Phase-reversing patterns						
Frequency (Hz)	2.5	5	10	20	30	40
Patient 1	0	0	1	1	0	0
Patient 2	0	0	0	1	0	0
Drifting pattern						
Velocity (deg/sec)	0.89	1.78	3.57	7.14	10.7	14.3
Patient 1	0	0.5	0	0	0	0
Patient 2	0	0	0	0	0	0

but otherwise each trial continued for 5 sec. In order to minimise the amount of paroxysmal activity induced a maximum of 3 trials per stimulus were given, and stimulus presentation was in order of increasing or decreasing pattern velocity. In this way, stimuli that were maximally epileptogenic were not presented until the extent of the patient's sensitivity to less epileptogenic stimuli had been established.

Results

The results are shown in Table III. Both patients were sensitive to the oscillating and phase-reversing patterns over a similar range of frequencies. There was only one isolated response to the drifting grating and this occurred at a pattern velocity different from that at which the oscillating patterns were most epileptogenic. Taking the data for the two patients together, over the entire range of frequencies or drift velocities, the probability of paroxysmal activity in response to a drifting grating is significantly lower than that in response to the other patterns ($\chi^2 = 4.92$, $P < 0.03$).

Discussion

The findings of both studies are in accordance with the predictions from the hypothesis that synchronisation of neuronal activity by the temporal rhythmicity of the stimulus contributes to epileptogenesis. Various alternative explanations of the results are possible, partly because it cannot be assumed that the extent of excitation produced by a drifting pattern is necessarily similar to that from an oscillating or phase-reversing pattern. Nevertheless it is fair to assume that, whatever the extent of excitation from a drifting grating, the excitation will not be grossly synchronised. In so far as the majority of patients had normal vision interictally, the excitation that precipitated the discharge was presumably a normal response to visual stimulation. Sensitivity to the drifting grating was considerably less than that to a static grating and so the most parsimonious explanation would attribute this difference to the failure of the stimulation to provide a temporal patterning in the excitation it induced.

The abolition of pattern sensitivity by drifting movement was almost complete. Indeed, the small residual effect could simply be due to synchronisation produced by changes in ocular fixation, although in the recordings made there was no indication of an association between eye movements and discharge.

Although photosensitivity is statistically associated with primary generalised epilepsy, few of our photosensitive patients had epilepsy of this type because it is comparatively rare in specialised epileptological practice. There were no differences between diagnostic groups in respect of the findings reported here or in our previous studies which

show no differences between patients with primary generalised epilepsy (and presumably anatomically normal brains) and those with secondary generalised or partial epilepsies (implying diffuse or focal cerebral pathology) (Wilkins et al. 1979, 1981; Binnie et al. 1981).

The findings do not permit the conclusion that temporal organisation is necessary for visual sensitivity but they do suggest that synchronisation of neuronal activity by the stimulus is an important contributory factor. It remains to be seen whether similar mechanisms obtain in other types of epileptogenesis.

Résumé

Mécanismes de l'épileptogenèse dans l'épilepsie photosensible induite par les effets de patterns mobiles

On a suggéré que le déclenchement de décharges EEG épileptiformes par un pattern dépendait de l'intensité de l'excitation dans le cortex visuel. On étudie ici le rôle de la synchronisation de l'activité des neurones par le stimulus. Chez 10 sujets sensibles aux patterns les effets des formes suivantes ont été comparés: (1) grilles immobiles, (2) grilles oscillant dans une direction orthogonale aux lignes (lesquelles devraient synchroniser l'activité dans les unités corticales sensibles à la direction), et (3) grilles défilant à la même vitesse angulaire (lesquelles ne produiraient pas de synchronisation ou bien alors une faible synchronisation, car les contours entrent et sortent des champs récepteurs des neurones de façon asynchrone). Les grilles oscillantes ont été le plus épileptogènes et celles défilantes le moins. Chez deux autres sujets, les patterns oscillants et à renversement de phase ont été plus épileptogènes que les grilles défilantes. Bien que d'autres explications soient possibles, ces résultats corroborent l'hypothèse que la synchronisation des neurones corticaux individuels par un stimulus contribue à l'épileptogenèse chez les sujets photosensibles.

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