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Effects of LSD on the Responses of Single Units in Cat Visual Cortex

D. Rose and G. Horn

University of Bristol, Department of Anatomy, The Medical School, Bristol BS8 1TD, England

Summary. The effects of intravenous doses (200 μg) of LSD on the activity of single neurones in the primary visual cortex have been studied in cats anaesthetized with urethane. Cells were stimulated with a bright bar of light moved over the receptive field, and orientation tuning was assessed quantitatively before and after administration of the drug. Changes in neuronal activity were compared with those observed in a control sample of cells recorded when the cats were given no drug. LSD increased the responsiveness of some cells to visual stimuli and decreased that of others, but some cells were not affected. The changes in responsiveness were dose dependent; the larger doses of the drug (expressed in μg/kg body weight) tended to depress the responses and the smaller doses to enhance them. The effects appeared earlier in complex cells than in simple cells. Changes in spontaneous activity, direction selectivity and orientational properties were found in some cells.

Key words: LSD – Visual cortex – Single units – Receptive fields – Sensory processing

Introduction

Disturbances of behaviour occur following administration of lysergic acid diethylamide (LSD) to cats and monkeys (Evarts, 1958). When this drug is taken by humans, the subjects describe a variety of effects, including illusions and distortions of sensory perception (Hoffer and Osmond, 1967). The way in which the drug acts on the central nervous system to produce these effects is not known. Since the disturbances of human perception are mainly visual, one potentially fruitful approach to this problem is to analyse the ways in which the drug influences the electrical activity of neurones in the visual cortex. This approach is promising because activity in the visual cortex is necessary for, and imposes constraints on, visual perception.

Mouriz-Garcia et al. (1969) and Horn and McKay (1973) have investigated in cats the effects of systemic LSD on single cells in the dorsal lateral geniculate nucleus (LGN). They found that the responsiveness of some cells to

visual stimuli was increased and that of others decreased by the drug. Horn and McKay found that larger doses tended to increase the proportion of cells which were depressed. Moreover, the actions of the drug on spontaneous firing, on the responses evoked by a stimulus in the centre of the receptive field, and on the responses evoked from the antagonistic surround region, were not necessarily changed in the same direction nor to the same extent. Although it is plausible to suppose that these changes in the activity of the cells in the LGN will alter the receptive field properties of cells in the visual cortex, it is difficult to predict precisely what these changes will be. We have therefore studied directly the effects of LSD, administered by intravenous injection, on the responses of single cells in the primary visual cortex of the anaesthetized cat.

Methods

Adult cats weighing 2.0–3.6 kg (mean 2.74) were anaesthetized with 5.5–6.5 ml/kg 20% urethane, sometimes supplemented with 10 mg/kg sodium pentobarbitone, administered intraperitoneally. Additional doses of urethane (1 ml/kg) were given as required. The animal's rectal temperature was maintained at 36–38° C with an electric blanket, and its EEG and EKG were monitored. The trachea and the saphenous vein were cannulated. The eyelids and nictitating membranes were removed a few minutes after injecting lignocaine hydrochloride (2%) into the eyelids. Four sutures were passed through the sclera posterior to the limbus and tied to stainless steel rings clamped to the stereotaxic instrument in order to prevent eye movements; in some cats the cervical sympathetic nerves were also sectioned bilaterally. Atropine sulphate (1%) eye drops were applied to paralyse accommodation and to dilate the pupils, and 2 mm diameter artificial pupils were substituted. Zero-power contact lenses prevented corneal drying, and additional spectacle lenses focussed the eyes on an oscilloscope screen 57 cm away. The projections of the blind spots and the areae centrales were plotted with a reversible ophthalmoscope on to a sheet of graph paper placed on the face of the screen. A 2–3 mm diameter craniostomy was drilled above the cortical (area 17) projection of the areae centrales and filled with low melting point wax (38° C; Gurr Ltd.) to reduce pulsations of the brain and the dura. Tungsten microelectrodes insulated with epoxy resin (Horn, 1969) were lowered through the wax and the intact dura into area 17 to record units extracellularly. Electrolytic lesions were sometimes made through the electrode at the end of the penetration to aid histological reconstruction of the electrode tracks.

Minimum response fields (Barlow et al., 1967) were plotted in each eye separately, by projecting stimuli on to a sheet of graph paper held to the oscilloscope screen. The cells were classified from their response fields into simple and complex types (Hubel and Wiesel, 1962). A few (< 20%) of these cells responded to stimuli at any orientation presented through either eye, although quantitative analysis revealed there was usually a clear preferred orientation and sometimes a preferred direction of movement. When there was some doubt about orientation specificity, cells could still be divided into simple or complex types on the basis of their other properties (Hubel and Wiesel, 1962).

The response field in the dominant eye was then selected for quantitative analysis. Bright bar stimuli were generated on an oscilloscope (Lan-Electronics Ltd.) by a PDP-12 computer (Digital Equipment Corp.). The background luminance was about 5 cd m^{-2} and the bar was about 1 log unit brighter. The bar was usually about 8–12 deg long and $^1/_4$ deg wide, but for some cells these dimensions were adjusted to improve the magnitude of the response. The number of times the cell fired as the bar crossed the field was counted by the computer. The velocity of movement was set to be somewhat faster than the velocity which gave the greatest number of spikes (Movshon, 1975). Having thus set up the optimal stimulus conditions, one or several orientation tuning curves were constructed, using a method designed to minimise the effects of any fluctuations in the tuning curve which may occur over time (Horn et al., 1972; Henry et al., 1973; Rose and Blakemore, 1974). The bar was swept across the response field once and then blanked out. After an interval of 5–12 sec, commonly 6–8 sec, the bar was moved across again at a different orientation, or some-

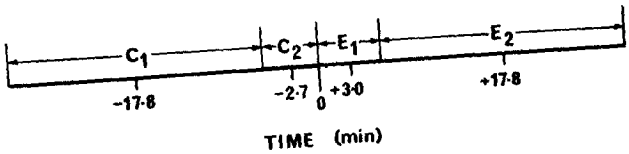

Fig. 1. Experimental procedure. During the first control period C_1 an orientation tuning curve was constructed. During periods C_2 and E_1 the cell was stimulated at the preferred orientation only. During E_2 another orientation tuning curve was constructed. The times shown are the mean values of the mid-points of each sampling period, i.e. the times half-way through each period, averaged over all the cells. The injection of LSD commenced at time = 0

times it was moved back at the same orientation before the orientation was changed for the next sweep. The orientation was altered in steps of 5–30° (usually 20°) systematically right around 360° until all orientations had been presented moving in each direction once (or twice if the return sweep was included). Then the orientation was rotated in the opposite direction so that the same orientations were presented in the reverse order. Thus the orientation might swing first anti-clockwise, then clockwise, then anti-clockwise and so on until the bar had been presented at each orientation moving in each direction 8 times. The orientation at which the changes in direction of rotation occurred was normally at about 90 degrees to the preferred orientation of the cell. For some cells stimuli were presented only over the range of orientations to which the cell responded. Blank sweeps of the bar were inserted after every 7–20 stimulus presentations to assess the spontaneous firing of the cell. The computer later calculated the mean number of spikes evoked by the stimulus at each orientation, corrected for the spontaneous firing rate. The orientation tuning curves were drawn out on a plotter (Calcomp 565). The mean time taken to determine a tuning curve was 18.1 min, the commonest procedure being to present 8×360° rotations in 20° steps. The orientation of the bar which evoked the greatest number of spikes will be called the *preferred orientation* and the mean number of spikes evoked by the stimulus at this orientation will be referred to as the *peak response*.

Since the effect of LSD on LGN cells is of variable duration, but may be quite short (Horn and McKay, 1973), it was necessary to devise a rapid method for detecting any effects of the drug on the response properties of the recorded unit. In addition, it was necessary to have some way of assessing what the response of the cells might be if LSD had not been given. It proved impossible to obtain a supply of the non-psychoactive (Cerletti and Rothlin, 1955) derivative of LSD, 2-brom-LSD, and so another type of control was used. Within these constraints the typical procedure was as follows. After a unit had been isolated an orientation tuning curve was constructed. This period of data collection is referred to as C_1 (see Fig. 1). The stimulus bar was then set at the preferred orientation and moved repeatedly in the preferred direction, usually with blank sweeps in between presentations; for some units, sweeps in the non-preferred direction were also included. This period of data collection is referred to as C_2.

If the peak response is stable from C_1 to C_2 then: (i) the difference between the two peak response values should be 0 and the mean of these differences (μ) for the 34 cells studied should also be 0: this mean, with its variance (s^2) and standard deviation (s), were therefore calculated; (ii) if the peak responses (x) recorded during C_1 are plotted against those recorded (y) during C_2 for each cell, the parameters of the regression equation $y = a + bx$ should be $a = 0$ and the regression coefficient, $b = 1$; (iii) the correlation coefficient between x and y should be 1.

Three min or more after period C_2 had begun, a dose of 200 µg of LSD was administered intravenously over 1 min. The bar continued to be presented at the set orientation for at least 4 min (period E_1) after the injection was completed. If the peak responses are not affected by the drug then the differences between the responses before (C_2) and after (E_1) the injection should be the same as those between the 2 control periods. Furthermore, if the responses recorded for each cell before and after the injection are stable then all the predictions set out in the preceding paragraph should also be met. If the cell was still present after period E_1 a complete orientation tuning curve (experimental data, late period, E_2) was reconstructed using identical stimulus presentations to

those used to obtain the first tuning curve during period C_1. The responses during E_2 were compared with those during C_2, to bars at the same orientation, using the method of analysis described above.

In addition to comparing the peak responses obtained during E_2 with those obtained immediately before injecting the drug (period C_2) the range of orientations to which the curve responded before (period C_1) and after (E_2) the drug had been injected were compared. This was done by subtracting the range of orientations to which the cell responded during C_1 from that during E_2. In order to decide what the expected differences would be if LSD were without influence, 2 successive tuning curves were obtained for each of 11 cells without giving the drug between the successive plots.

Whenever possible a succession of curves was taken from the cells to see if any recovery from the effect of the drug was occurring.

Only 1 dose (200 µg) per cat (between 56 µg/kg and 100 µg/kg) of LSD was used, and this dose was selected because it is known (Horn and McKay, 1973) to influence the responses of the cell in LGN and it is not associated with any consistent changes in blood pressure or EEG. After studies of one cell had been completed LSD was not given again for at least 2 hours (usually much longer) after the preceding injection.

The effects of the drug were determined on 25 cells in 8 cats. 18 of these cells (8 simple, 10 complex) were held long enough to complete a second tuning curve during the later period (E_2; Fig. 1) after drug injection. The cells studied had receptive fields centred from 0–10 deg from the projection of the area centralis.

Results

Analysis of Changes in Peak Response

Control Data (Table 1, Columns 1, 5)

The peak responses were stable from one control period to the other for all cells.

Experimental Data (Table 1, Columns 2, 3, 4)

The influence of the drug varied from cell to cell: this influence is reflected quantitatively by an increase in the value of s^2 compared with that for the controls. The effect varied also according to the receptive field properties of the cell. As for the control data, the values of μ were not significantly different from 0. This finding was valid for the comparison of data from control period C_2 with those obtained from the early experimental period, E_1 as well as with those from E_2. Therefore LSD did not have a *uniform* effect, either of depression or excitation on the cells.

Cells with Complex Fields (Figs. 2B, 3). The variance of the differences between the peak responses recorded immediately before the drug (period C_2) and immediately after (period E_1) is $s^2 = 18.49$: the corresponding variance from the controls (periods C_1 and C_2) is $s^2 = 2.02$. These variances are significantly ($F = 9.15$; $p < 0.005$) different. The increase in the variability of the responses which followed the injection of LSD is also reflected in the lowering of the correlation coefficient, r, relative to its value in the control conditions

Table 1. The data set out in this table refer to peak responses. The results are set out according to the receptive field properties of the cells studied. The origins of the sets of peak responses that were compared are set out at the top of each numbered column of data. Columns 1, 2 and 3 refer to results from all units recorded over the corresponding periods; whereas 3, 4 and 5 refer to results from the 18 units which were recorded over all of the periods C_1 to E_2 (see text). See *Methods* for definitions of statistics. Note that in column 4, complex cells, r ceases to be significant

Statistic	1 C_2 v C_1	2 E_1 v C_2	3 E_2 v C_2	4 E_1 v C_2	5 C_2 v C_1
Complex cells					
Mean difference (μ)	−0.54	−0.60	−0.17	−0.79	0.34
Standard deviation (s)	1.42	4.30	3.53	4.73	1.21
Regression parameter a	0.88	2.98	2.17	–	0.06
Regression parameter b	0.86	0.62	0.77	–	0.98
Correlation coefficient (r)	0.95	0.59	0.76	0.59	0.97
Significance level	0.001	0.05	0.01	n.s.	0.001
No. of cells	17	12	10	10	10
Simple cells					
Mean difference (μ)	0.06	−0.49	3.30	−0.53	−0.54
Standard deviation (s)	1.41	1.48	10.08	1.68	1.72
Regression parameter a	−0.07	0.09	–	0.49	−1.09
Regression parameter b	1.02	0.93	–	0.90	1.03
Correlation coefficient (r)	0.98	0.97	0.54	0.98	0.90
Significance level	0.001	0.001	n.s.	0.001	0.005
No. of cells	17	13	8	8	8
Total no. of cells	34	25	18	18	18

(Table 1, columns 1 and 2). Although r is still significantly different from 0 for the peak responses before and after the drug, the lowering of its value is also significant ($p < 0.005$). Thus, although the response amplitude before the drug was given is predictive of the response immediately afterwards, the reliability of the prediction is much weaker than it would be if no drug had been given.

The effects persisted during the period E_2 ($s^2 = 12.46$ for E_2 v C_2; s^2 for C_2 v $C_1 = 2.02$; $F = 6.17$, $p < 0.005$), but were becoming weaker since the correlation coefficient (0.76) is no longer significantly less than that for the control samples (0.95). The attenuation of the effects of the drug with time on one cell are illustrated in Figures 2B and 3A.

Cells with Simple Fields (Figs. 2A, 4). The effects of LSD on the peak responses were delayed: no effect was observed during the period (E_1) immediately following injection. However, the variance of the differences between the peak responses of the later period E_2 and those of C_2 is 101.61. This value is significantly ($F = 51.06$, $p < 0.005$) greater than that ($s^2 = 1.99$) from the 2 control periods (C_2 v C_1). In addition, there is no correlation between the peak responses from C_2 and E_2: the peak response amplitude during C_2 is no longer predictive of the amplitude during the late post-injection period. As with the complex cells, some simple cells became more responsive (e.g. Fig. 4), some less responsive and the responses of others were relatively unaffected.

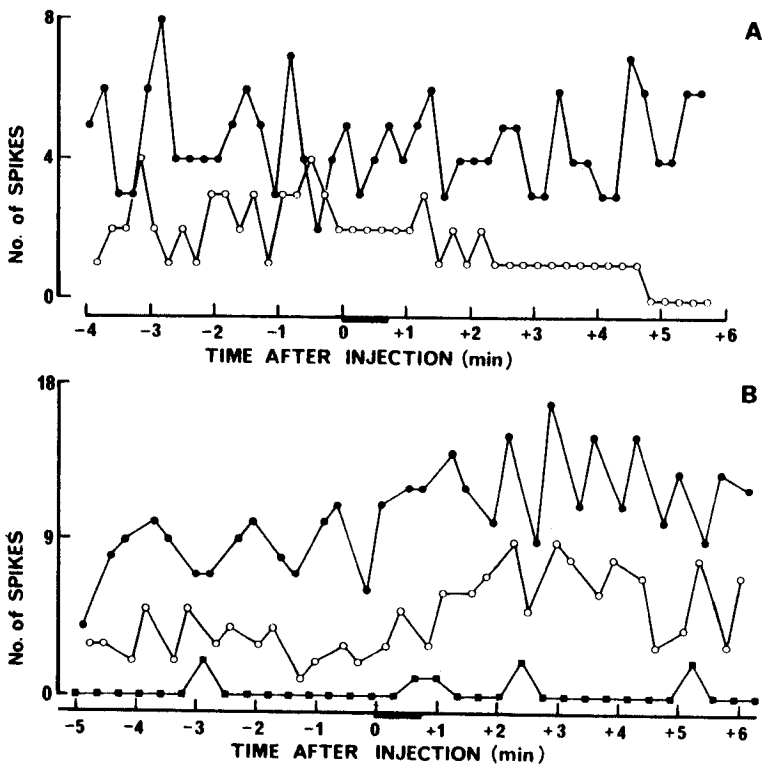

Fig. 2A and B. Immediate effects of LSD on the response to bars at the optimal orientation. The period prior to the injection is C_2, that just after, E_1 (Fig. 1). The thick bars on the abscissae indicate the periods of injections. **A** simple cell. **B** complex cell. Symbols show number of spikes counted in one gating period (4 sec in A, 2 sec in B). Filled circles: bar moved across receptive field in the preferred direction. Open circles: bar moved in non-preferred direction. Filled squares in B: spontaneous activity of cell for the 2 sec sampling period; spontaneous firing was absent for the cell of A

Fig. 3A and B. Orientation tuning curves of complex cells. The curves were taken before (period C_1: filled circles) and after (period E_2: open circles) LSD. The responses (means of 8 sweeps of the bar) are shown relative to spontaneous firing level as zero (dashed line). Corrected evoked discharge = mean number of spikes/traversal – mean number of spikes during blank sweeps. Thus when there is no response, the corrected evoked discharge is 0. Bars show standard errors. The distance below the dashed line of the arrows on the right gives the mean number of spikes per blank sweep, and thus the spontaneous discharge. The textures of the arrows match those of the points on the corresponding curves. Orientation code: 0° = vertical bar moving to the right; 90° = horizontal bar moving upwards; 180° = vertical bar moving to the left; 270° = horizontal bar moving down. **A** Cell which became more responsive after LSD. The stippled triangles show a further assessment of the curve plotted immediately after E_2. The responses plotted in this figure and Figure 2B were derived from the same cell. **B** Cell which became less responsive after LSD. Note the lack of effect on the inhibitory regions of the tuning curve

Peak responses were obtained in the late experimental period for only 8 simple and 10 complex cells. These numbers are smaller than those available for the other comparisons. Because it is possible that the reduction in numbers would alone influence the significance levels, the above computations were repeated using data from only these 8 and 10 cells respectively (Table 1, columns

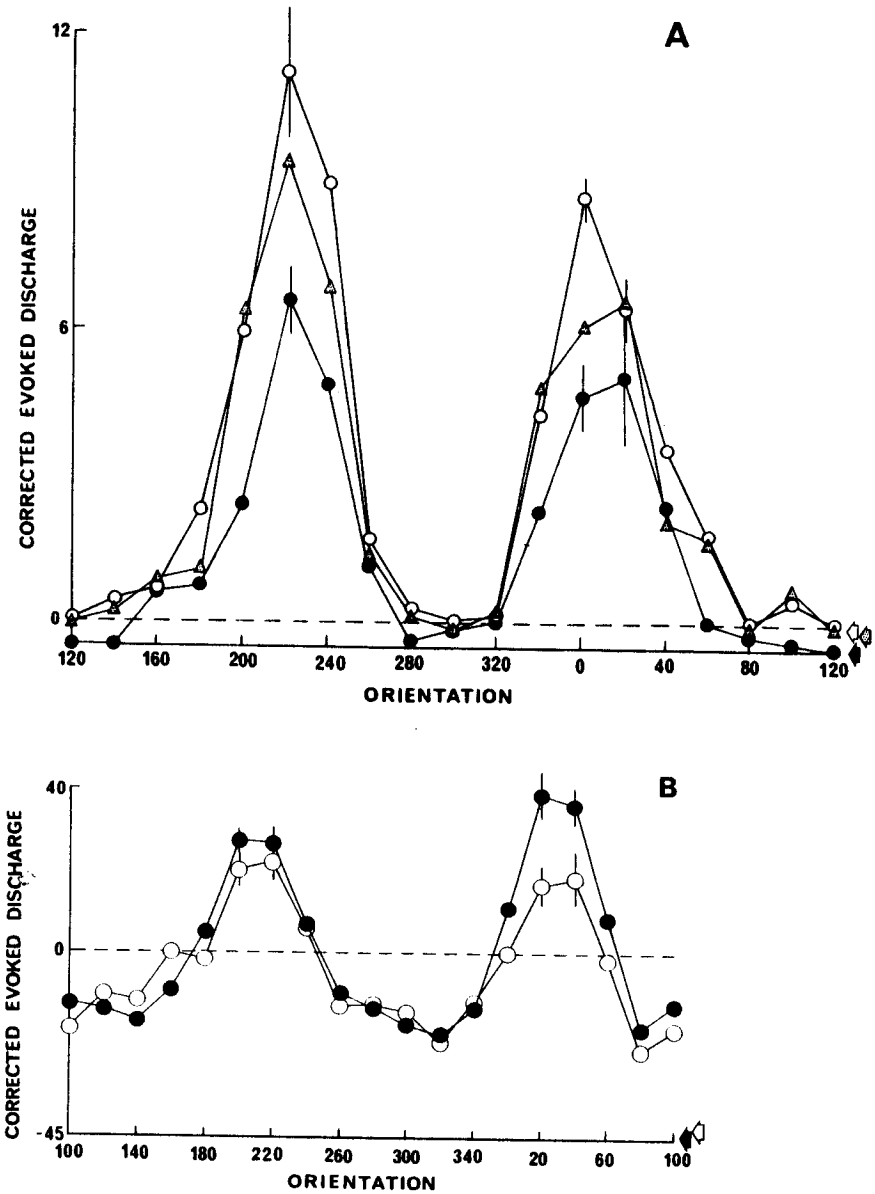

Fig. 3A and B

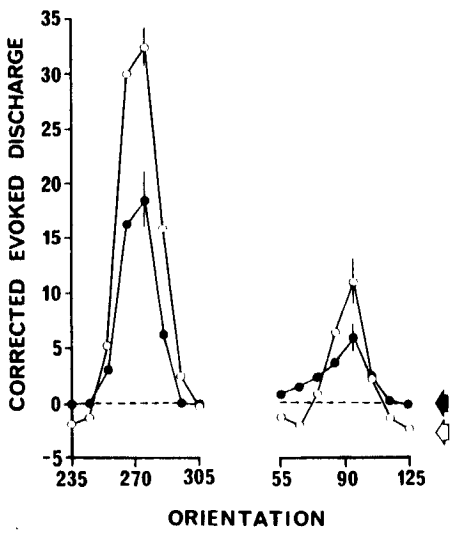

Fig. 4. Orientation tuning curves of a simple cell. Conventions as in Fig. 3 (solid symbols = before LSD; open = after). This cell was only stimulated over the range of orientations to which it would respond, instead of at all orientations as was done for most cells. Responsiveness was increased after the drug

4 and 5). With only one exception, none of the results that are significant with the larger number of cells cease to be so with the smaller number.

There is a significant ($p = 0.05$) negative correlation between dose (expressed in μg/kg of body weight) and change in peak response for data from C_2 and E_2. This finding is valid both for simple and complex cells. There was a tendency for the peak response to be increased at lower doses and decreased at higher doses.

Analysis of Other Parameters of Unit Activity

Direction Selectivity. The effects of LSD on the response to the bar set at the optimal orientation, but moving in the non-preferred direction varied from cell to cell. In the majority of cells, and in both early and late experimental periods, the changes in response to the non-preferred direction of movement paralleled those to the preferred (e.g. Figs. 2B, 3A, 4). In other cells (e.g. Fig. 3B) small differential effects occurred, and in 2 cells the differential effects were marked (e.g. Fig. 2A).

Inhibitory Flanks. An inhibitory region was occasionally seen on either side of the optimal orientation. This flank was variably affected by the drug, and independently of the effects on peak responsiveness (Figs. 3, 4).

Orientation Range. The range of orientations over which a cell responded could be judged by eye, from the plot of the tuning curve, to an accuracy of about 10–15% of the total range. Because only 11 control comparisons of tuning curves were available cells with simple and complex fields were not analysed separately. The peak difference between the 2 sets of control curves was $-2.9° \pm 9.8°$ (S.D.); that between the experimental and control curves was $+2.2° \pm 16.9°$. The mean difference is not significantly changed in the drug

condition, but the variance is increased ($F = 2.97$; $p < 0.05$). Changes in orientation range were correlated ($p < 0.05$) with changes in peak response (e.g. Figs. 3 and 4).

Spontaneous Activity. For most cells the spontaneous level of firing was very low or nil. In some cells the maintained discharge increased after LSD (Fig. 4), in others it was unaffected (Figs. 2B, 3B) and in others it decreased (Fig. 3A). The changes were sometimes, but not always, accompanied by changes in the peak response; conversely, the peak response sometimes changed when spontaneous activity was unaffected. When both parameters were affected, the changes tended to be in the same direction: large increases in one were never accompanied by large decreases in the other.

For all parameters of unit activity studied, there was no tendency for the effects of LSD on the first cell recorded in a cat to be different from the effects on cells studied subsequently in that cat.

Discussion

Systemic administration of LSD causes the responses of some cells in the visual cortex to increase, those of others to decrease, while some cells are apparently unaffected. This phenomenon is seen within a few minutes in complex cells and persists, although declining in strength, for at least half an hour or so. For simple cells, however, the effect builds up more slowly. Directionality may alter and there is a small effect on the range of orientations to which the cell will respond. The steps in plotting orientation tuning curves (commonly 20°) were too coarse to allow us to detect smaller influences (< 20°) of the drug on the position of the preferred orientation, although such effects may be present.

The mechanisms by which LSD affects the functioning of the visual cortex cannot, of course, be deduced from the results of the present experiments, since the drug was given intravenously and therefore reached many parts of the brain. It is likely that several transmitter systems are affected (e.g. Haigler and Aghajanian, 1974; Brimblecombe and Pinder, 1975; Creese et al., 1975). It is not known how LSD interacts with the anaesthetic used in this study (see Horn and McKay, 1973).

Among the effects of LSD on perception are distortions and apparent movement of objects: "They appeared to change shape and size and pulsated. Parallel lines or patterns became distorted, developed wavelike forms and moved as if covered with a layer of film or water" (Hoffer and Osmond, 1967, p. 113). If visual perception is in some way affected by the activity of the cells in the striate cortex then changes in the response properties of these cells may give rise to disturbances of visual perception. Many suggestions can be made to account for these disturbances in terms of changes in receptive field properties, but there is as yet no firm evidence in support of any one explanation.

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