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PROLONGED EFFECTS OF LSD ON EEG RECORDS DURING DISCRIMINATIVE PERFORMANCE IN CAT; EVALUATION BY COMPUTER ANALYSIS

W. R. ADEY, R. PORTER[1], D. O. WALTER AND T. S. BROWN

Brain Research Institute, University of California at Los Angeles, and Veterans Administration Hospitals, Long Beach and Los Angeles, Calif. (U.S.A.)

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INTRODUCTION

Psychotomimetic and hallucinogenic drugs exert their effect in man and animals for periods ranging from a few to many hours (Lear *et al.* 1959; Rothlin 1957). It has long been recognized that other more subtle mechanisms might also be involved, since the usual behavioral symptoms and electrophysiological effects fail to appear when the doses are repeated at intervals shorter than a few weeks (Adey *et al.* 1962), and cross-habituation has been reported between hallucinogenic agents having no close structural interrelations (Balistrieri and Fontinari 1959; Jarvik and Chorover 1960).

Evaluation of EEG changes in the acute phase of drug action has implicated deep structures of the temporal lobe, and particularly the hippocampal system, for both psychotomimetic agents, such as cyclohexamine derivatives (Adey and Dunlop 1960), and for hallucinogenic agents, such as LSD and its derivatives, in both cat and monkey (Adey *et al.* 1962; Monroe and Heath 1961). Both types of drugs induced large amplitude, seizure-like wave discharges in hippocampal structures. In the cat, the abnormal wave trains induced by LSD appeared in brief bursts beginning and ending abruptly, particularly in conditions of reduced visual and auditory environmental stimuli. Their persistence in behavioral test situations was associated with a disruption of the learned performance. This defective behavior was associated with the propagation of the abnormal hippocampal activity into a variety of subcortical centers (Adey *et al.* 1962).

[1] On leave from the University Laboratory of Physiology, Oxford, England.

As a first approach to the detection of subtle but consistent changes in patterns of EEG activity over a period of many days following a single dose of LSD, we have here examined the wave trains accompanying performance of a learned discriminative task, from test data recorded on days before, during and following the drug. Our previous studies have examined the characteristics of these wave trains by a variety of computing techniques, including averaging, correlation, cross-spectral and phase modulation analyses (Adey *et al.* 1960; 1961; Adey and Walter 1963; Walter 1963; Walter and Adey 1963). They have sought to establish the possibility of hidden patterns in the apparent imprecision of the EEG, on the premise that the slow, graded wave processes characteristic of cortical tissue might provide the basis for a signal system within cerebral structures, and perhaps relate to both transaction and storage of information characteristic of this tissue.

METHODS

Detailed data are presented here from six cats repeatedly exposed to LSD, psilocybin and psilocin (Adey *et al.* 1962). Data collected daily from these animals have been subjected to extensive computer analysis, with extended testing periods separating each dose of LSD. In this way, a very substantial baseline was secured, and each animal served in many respects as its own control.

Electrodes were chronically implanted in the dorsal hippocampi, the adjacent entorhinal (posterior pyriform) cortex, the amygdaloid complex, the subthalamus and the rostral midbrain reticular formation. Screw electrodes were placed over the primary visual cortex.

Behavioral training was performed in a modified T-maze, with approach to food on the basis of a visual cue. A 500 c/sec tone was presented during the approach. Its onset coincided with the opening of the doors of the start box, and it was terminated on completion of the approach. It served to orient the animal in the test situation early in training, and in continuing studies, allows separation of orienting from discriminative behavior. Forty test runs were performed each day, and only those approaches were rewarded which were directly to the side of the T-maze displaying the visual cue. All drug tests were conducted after attainment of a stable performance level in excess of 90% correct, and at a time when the animals might thus be regarded as over-trained. Solutions of LSD were prepared freshly for each experiment from crystalline material and administered by intraperitoneal injection. The doses were insufficient to grossly impair performance capability, even when tested 1 to 2 h after drug administration.

Primary records during the experiment were obtained on a Grass 8-channel electroencephalograph. Electrical gates for the determination of epochs in the behavioral test paradigm were also used to initiate the averaging epoch of 2.0 sec in an average response computer (Mnemotron CAT). Initiation of the averaging analysis was arranged to precede presentation of the behavioral test situation by either 70 or 250 msec on each trial. Completion of the approach occupied approximately 1.2 sec. The output of the CAT computer was displayed on a chart recorder at the end of 20 and 40 approaches on each test day. Further analysis of these computed averages by auto- and cross-spectral computation required their transfer to an appropriate digital form for presentation to an IBM 7094 computer in the adjacent Health Sciences Computing Facility.

RESULTS

A fixed dose level of LSD of 70 to 80 μg/kg by intraperitoneal injection was used in all experiments. The absence of major effects on task performance in the period 1 to 3 h after this dose of LSD (Adey *et al.* 1962) was confirmed. Performance defects at this time occurred sporadically, and were consistently related to occasional induction of seizure-like episodes in the EEG. Sample "resting" records, taken immediately prior to testing in the T-maze, were compared for days before and after LSD with those taken 1 to 2 h after injection of LSD. Visual inspection as well as auto- and cross-spectral analysis of the resting records have failed to reveal significant changes in hippocampal, subcortical or visual cortical leads which might be attributable to the drug. As will be described below, the computed averages from the dorsal hippocampus during discriminative performance were, however, considerably modified in the days following LSD. The gradual increase in the regularity of the computed average of these wave trains associated with attainment of higher performance levels during training has been discussed in detail elsewhere (Adey and Walter 1963). Since these previous studies indicated that the computed averages of epochs immediately prior to presentation of the test task were irregular and of small amplitude, the test situation was presented either 70 or 250 msec after commencement of the computer analysis epoch. This permitted a more extended display of events occurring up to almost 2 sec from the moment of task presentation.

a. *Effects in hippocampal records*

(i) *Comparison of effects in bilateral leads; typical hippocampal records.* Tracings from the left and right dorsal hippocampus (LDH, RDH) in the course of the discriminative performance are shown in Fig. 1. In control records 6 days prior to receiving LSD (*A*), the RDH record showed a typical regularization at about 5.5 c/sec in each of the seven tests shown during approach to the food reward. By comparison, the records prior to commencement of the approach were essentially irregular, with slower dominant frequencies in the range 2 to 3 c/sec. These RDH records are typical of those obtained from the dendritic layer of the pyramidal cells. Those from the LDH, from a less optimally placed recording dipole, showed considerably less induced regularity during the period of discriminative approach. Similar records during the task performance 2 h after LSD (*B*) and 3 days later (*C*) suggested a modest increase in regularity in LDH, but little else to distinguish these

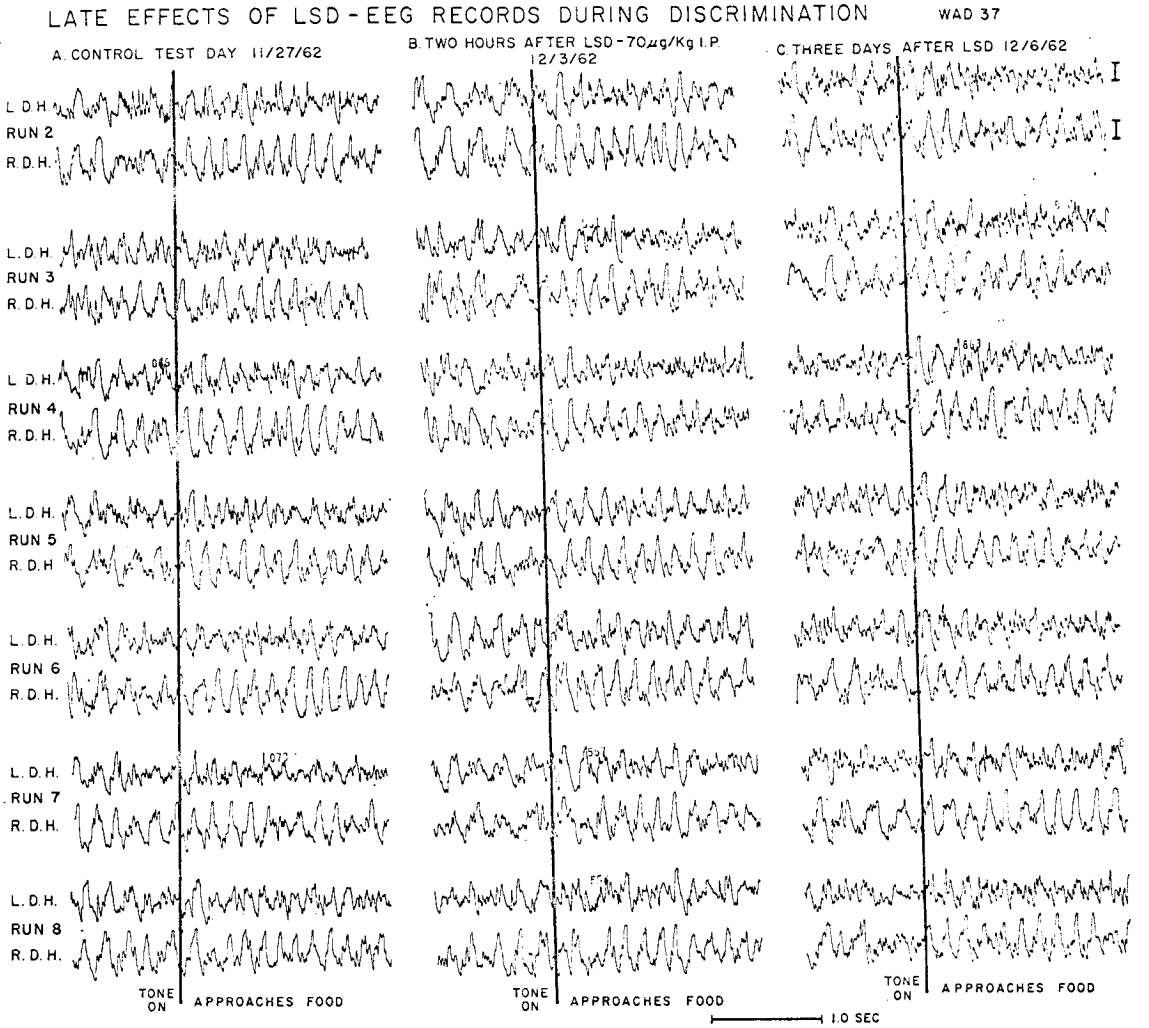

Fig. 1

Typical records from left and right dorsal hippocampi (LDH and RDH) in a cat during approach to food reward. Typical regularization of theta wave trains occurred during each discriminative performance. Presentation of task and onset of reinforcing tone are indicated by vertical lines. Calibration 50 μV.

records from the controls.

The computed averages from the RDH were markedly different in comparisons of pre- and post-drug trials (Fig. 2). In control records (*A*), the regular average during the approach typically rose in a gradual fashion to a maximum and declined thereafter in a relatively regular fashion. The envelope of the average exhibited a "spindle" shape. Similar averages on days after LSD (*C*) were characterized by a greater amplitude with the maximum occurring typically in the initial waves immediately following presentation of the situation, and with a slower and more regular decline than in control records. This modification persisted for 5 days after LSD. LSD appeared to induce increased rhythmic discharges also in the LDH lead, an inference from the EEG records amply confirmed by the computed averages of wave trains during the discriminative performance (Fig. 2).

(ii) *Corroborative evidence of late changes in hippocampal structures of other animals.* All six

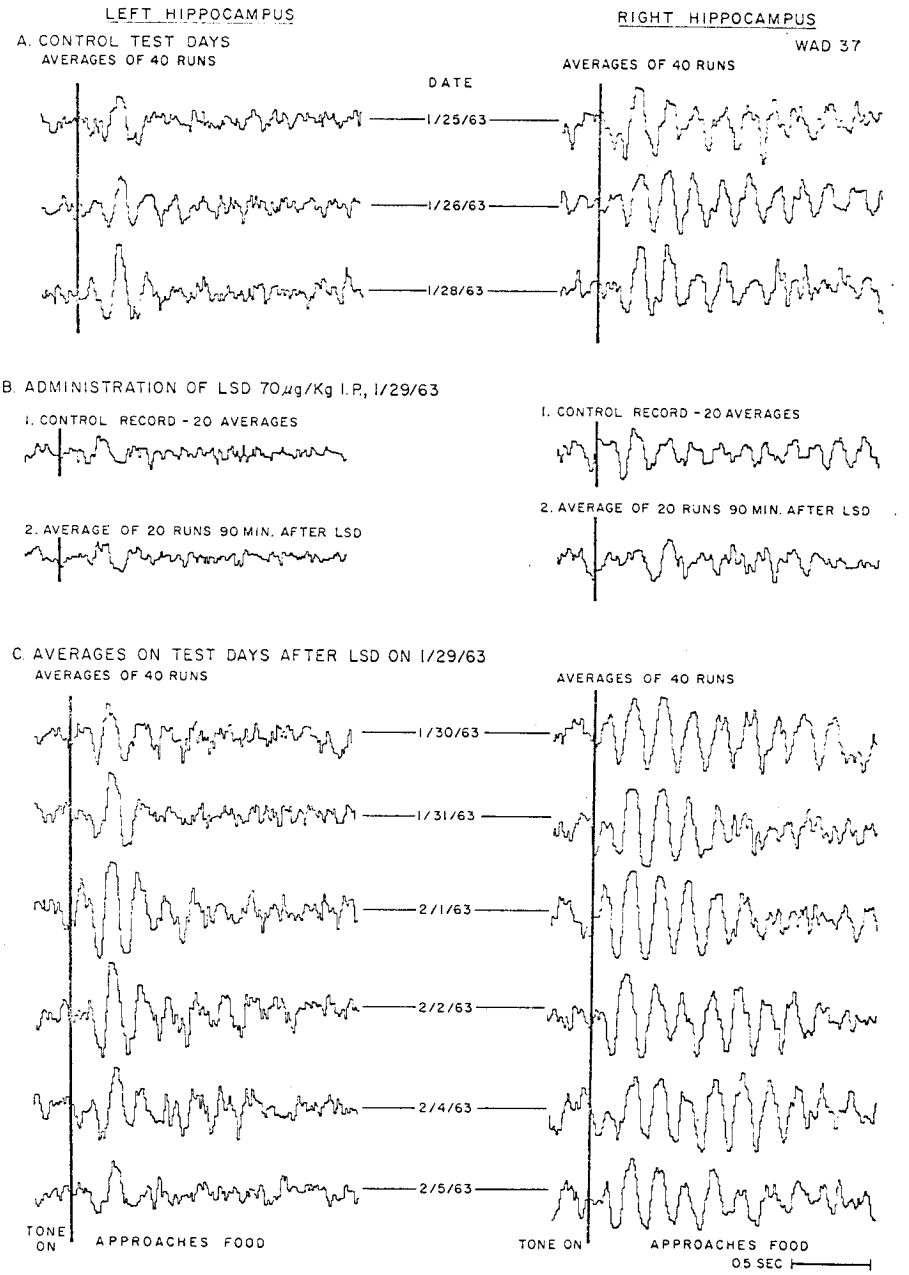

Fig. 2

Computed averages of epochs of left and right hippocampal EEG records during approach performance on days before LSD (*A*), the day of LSD dosage (*B*), and days after LSD (*C*). There was an increase in the amplitude and regularity of the averages following LSD. This maximized 3 days after the drug (*C*, 2/1/63), and declined thereafter.

animals in the present study showed persisting effects of LSD in hippocampal records after both initial and later injections. Representative records from two additional animals are shown in Fig. 3.

Our previous studies have indicated that hippocampal records from cats show considerable individual variations in the inherent regularity of the theta activity. The minority of

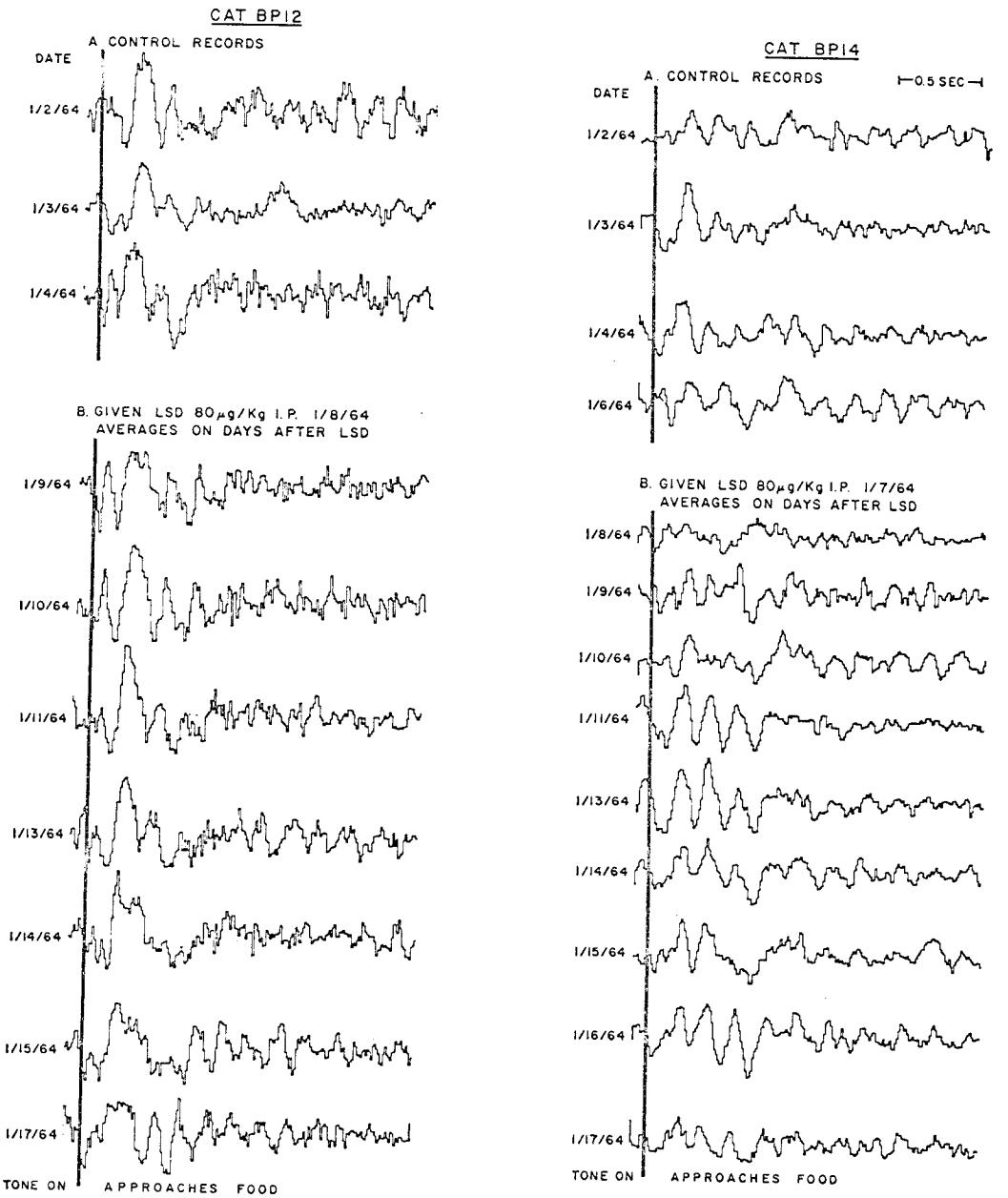

Fig. 3

Averages of 40 daily trials in dorsal hippocampal leads from two different cats before (*A*) and following (*B*) intraperitoneal LSD 80 μg/kg. (Cat BP 12 had received one previous dose of LSD 71 days before *B*.) In cat BP 12, there was an increment in amplitude and regularity of early waves in the average 2 days after the drug (1/10/64) which declined in the ensuing 3 days. In cat BP 14, similar effects occurred 4 to 6 days after the drug (1/11/64 to 1/13/64). This drug test in BP 14 followed 48 days after electrolytic lesions in hippocampal tissue adjacent to the recording site, but without apparent modification of drug action.

subjects exhibiting irregular or essentially arhythmic theta activity in intertrial intervals rarely showed a prolonged sinusoidal theta burst as a concomitant of the discriminative task. Com-

puted averages from such animals usually showed some regularity during the approach (Fig. 4, *A*), at dominant frequencies around 2 to 4 c/sec. LSD initially reduced the amount of these slow components for 2 or 3 days after the drug, followed, 4 days later, by a period in which they were enhanced in comparison with control records (Fig. 4, *B*).

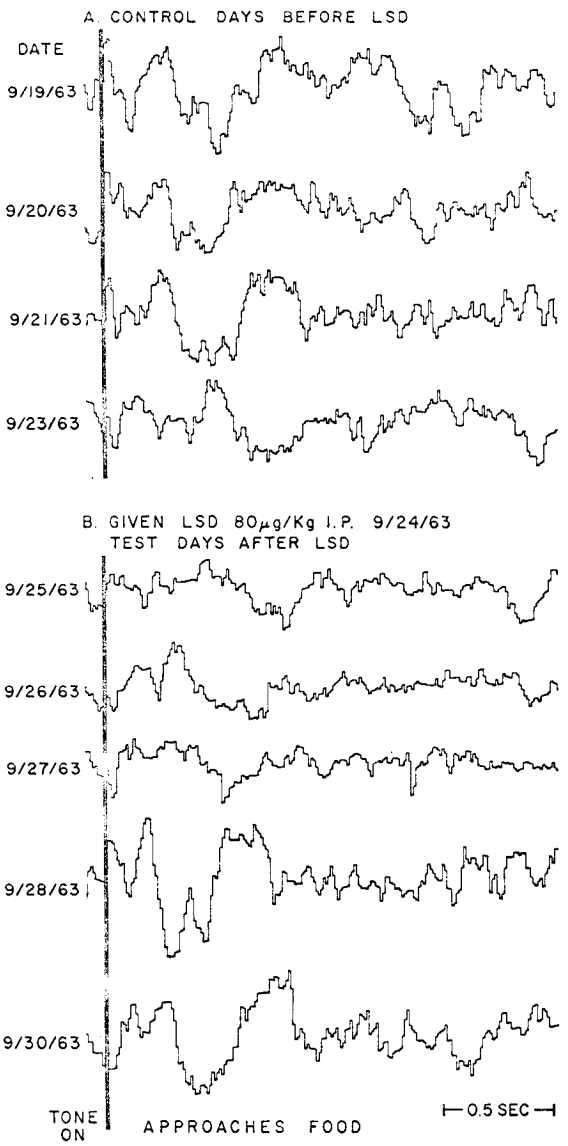

Fig. 4

Averages of 40 daily trials in a dorsal hippocampal lead exhibiting essentially irregular activity in the EEG records. As in more regular EEG records, the average showed increased amplitude in early waves 4 and 6 days after LSD (9/28/63 and 9/30/63).

(iii) *Comparison of LSD effects in closely adjacent hippocampal leads.* In a series of animals with bilaterally implanted linear arrays of six hippocampal electrodes transversely aligned and spaced 1.5 mm, it has been possible to observe differences appearing in adjacent recording dipoles in their late responses to LSD. In Fig. 5 computed averages in the left column are from a pair of electrodes located medially in the hippocampus (zone CA 1 of the pyramidal cell layer); those in the right column are from an immediately adjacent pair lateral to the first, and sharing one electrode with it. In control records (*A*), the theta activity averaged at a smaller amplitude in the medial electrode pair than in the lateral. Although the animal's behavioral performance at this time was around the 100% level, the time from commencement of the task at which the computed average peaked in amplitude clearly varied from day to day, particularly in the lateral electrode pair. For 4 days after LSD (*B*), the averages from the medial pair exhibited a sharp increase in amplitude and regularity, particularly in the initial waves of the train, and declined to control levels thereafter. The averages from the lateral leads suggested decreased rhythmicity after LSD, when the medial dipole showed maximum regularity. The anatomical location of these dipoles may provide a basis for discussion of the findings.

b. *Late effects of LSD on computed averages from extra-hippocampal structures*

On the basis of previous studies (Adey *et al.* 1961), we have examined the effects of LSD on patterns of rhythmicity in averages from the pyriform cortex and reticular formation.

(i) *Posterior pyriform (entorhinal) cortex.* Computed averages of wave trains in the entorhinal cortex after the third dose of LSD were less obviously modified than in the hippocampus (Fig. 6). This dose followed 79 days after the first, and 59 days after the second. There was an increase in the amplitude of the average in the early waves at the commencement of the discriminative performance, but little evidence of a sustained increase in regularity in the later parts of the approach epoch. This increment in regularity was maximal 4 days after dosage with LSD (Fig. 6, 10/22/62) and subsequently declined

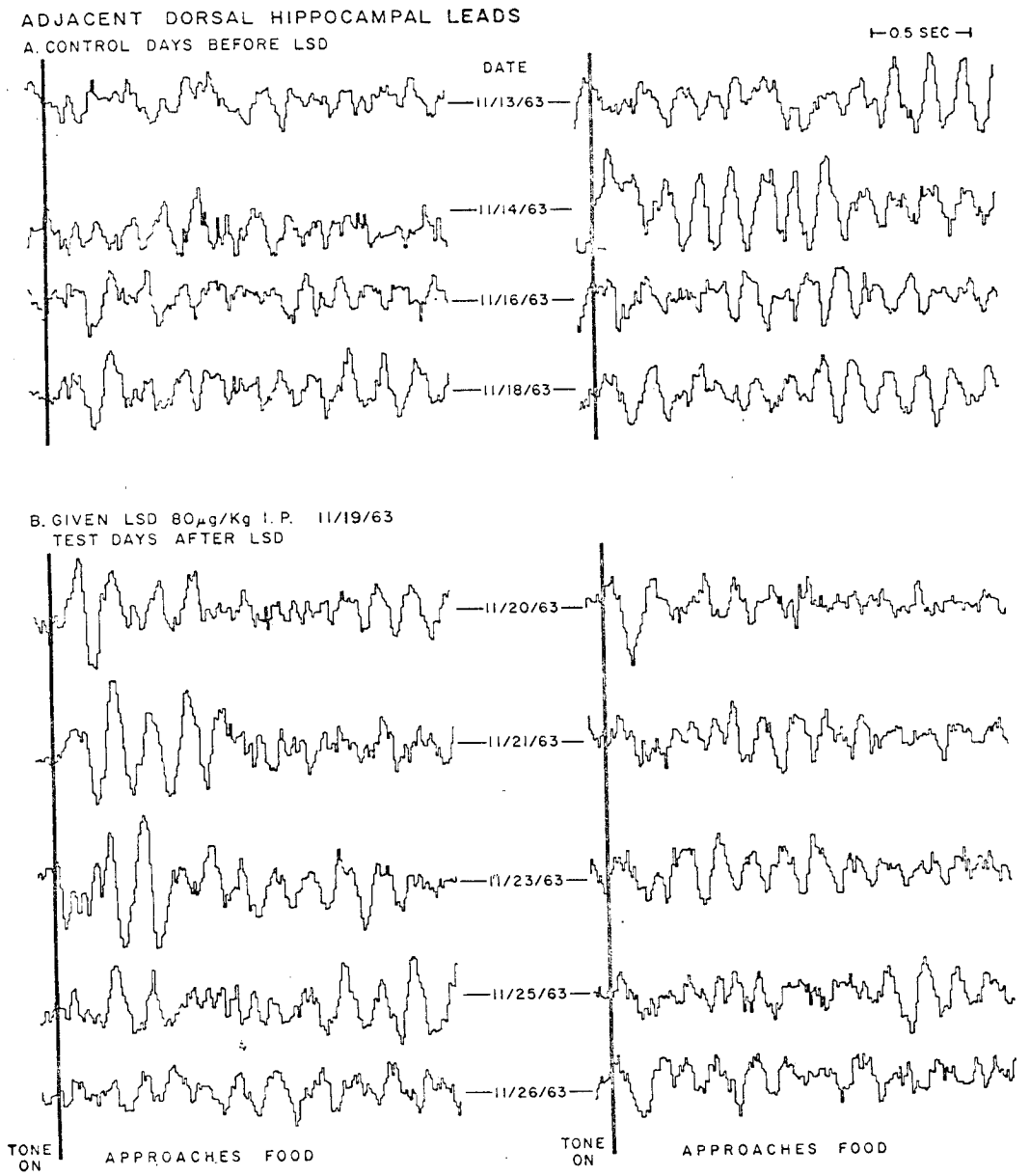

Fig. 5

A comparison of simultaneous averages from adjacent bipolar records in the vicinity of region CA 1 of the dorsal hippocampus (see text). In control averages (*A*), the more medial dipole (left column) was characterized by a small amplitude rhythmicity in comparison with the lateral dipole (right column). After LSD, there was a sharp increase in amplitude and regularity in the average from the medial dipole, but little change in the lateral one.

toward control levels.

(ii) *Midbrain reticular formation.* Similar averages of activity in the midbrain reticular formation on the days before, during and following the first dose of LSD were also examined in the same animal (Fig. 6, left). In *B*, the average of 20 runs made 110 min after LSD showed only rapid, irregular small amplitude components indicating that the large amplitude slow waves seen in the EEG (Adey and Walter 1963) were

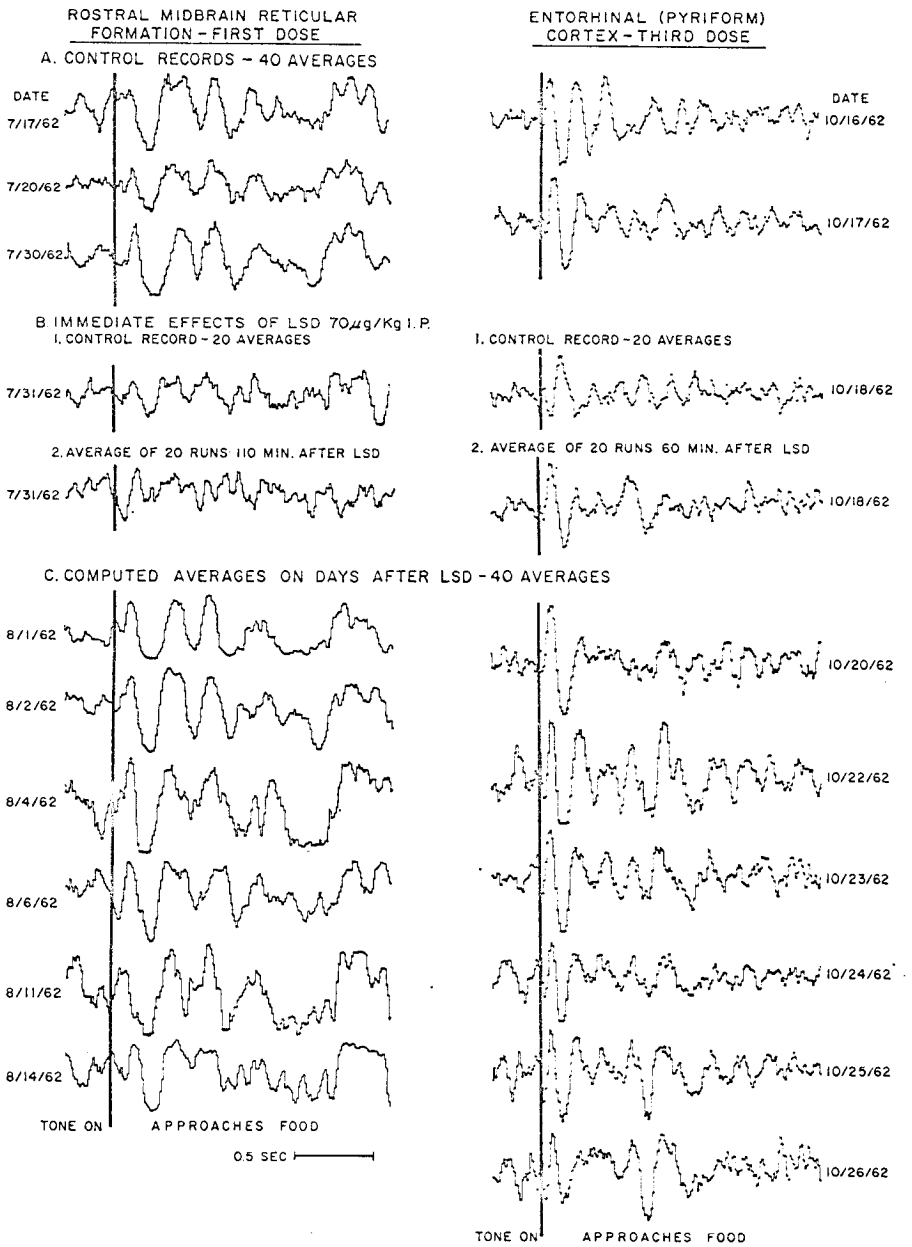

Fig. 6

Computed averages of midbrain reticular and enthorhinal cortical activity, preceding (*A*), during (*B*) and following (*C*) a single dose of LSD. Each average was for 40 approaches in the same cat (BA 15).

insufficiently phase-locked to the moment of presentation of the test situation to appear in the computed average. Small but regular wave trains were seen in control records immediately prior to dosage with LSD (*B*).

Only minor differences were detected between the pre- and post-LSD averages in respect to the train of three waves characterizing the initial part of the approach epoch. Only the late wave component of the average (about 1.2 sec after initiation of the approach) seemed to increase and to remain in excess of its amplitude in

control averages for at least 12 days after LSD. Its onset was essentially coincident with attainment of the food reward. It was absent from the average immediately following LSD, and gradually reached a maximum 4 days later (Fig. 6, *C*, 8/4/62).

DISCUSSION

This study has attempted to provide information on two important questions relating to the well known behavioral tolerance following a single dose of LSD. Firstly, we have attempted to detect lasting EEG changes and to relate their persistence to the time course of the tolerance following a single dose of LSD. Secondly, in view of the differential susceptibility of certain temporal lobe systems to LSD and related hallucinogenic agents (Adey *et al.* 1962; Monroe and Heath 1961), we have compared magnitude and persistence of these changes in the hippocampus with those in the rostral midbrain reticular formation, with which the hippocampal system is substantially interrelated (Adey *et al.* 1957).

This study has clearly indicated that a single dose of LSD can induce changes in the computed average of hippocampal theta trains accompanying the discriminative performance, and that these changes reach a maximum about 4 days after the exposure. Such increased regularity induced by LSD appears to decline more rapidly, however, than the tolerance to a second dose, which appears to last 2 or 3 weeks in the cat (Adey *et al.* 1962). It is possible that more subtle electrophysiological changes may persist longer than noted here. The averaging technique used here can reveal with exquisite sensitivity the degree to which either theta wave trains or evoked transients may show phase-locking to the presentation of successive behavioral tasks. Our attempts to disclose more subtle changes with auto- and cross-spectral analysis have been so far unsuccessful.

This study has also shown a differential susceptibility of different brain regions to LSD. Although the sampling from different regions has been small, the findings suggest that the induced rhythmic modifications, best developed in the hippocampus, were less obvious in the adjacent pyriform cortex. Within the former, differences in averages from adjacent dipoles in the vicinity of CA 1 may relate to the termination of both temporo-ammonic and alvear pathways in this region and in the adjacent subiculum. In the midbrain reticular formation, there was little effect on the rhythmic waves of the primary train immediately following task presentation. The regional susceptibility to late effects of LSD thus appears to follow a substantially similar distribution to the acute changes following LSD, in which spontaneous seizure-like discharges make their first appearance in the hippocampal system and propagate in a dose-dependent fashion to the nucleus ventralis anterior, subthalamus and rostral midbrain reticular formation (Adey *et al.* 1962; Monroe and Heath 1961). A basically similar pattern of propagation of electrically induced hippocampal after-discharges was described in the monkey by Poggio *et al.* (1956).

The biochemical basis for these prolonged effects remains elusive. In recent years much attention has been directed to the biologically active amines (Brodie *et al.* 1955, Brodie and Costa 1962) as the substrate for many of the effects of both tranquillizing and hallucinogenic substances. It has been inferred that the lasting sedative effect related to changes in brain serotonin concentration, rather than to the concentration of reserpine. Shore *et al.* (1955) have reported an interaction between serotonin and LSD in the central nervous system, with reduction of serotonin-induced sleep following hexobarbital anesthesia in the rat. Their doses of LSD (10 mg/kg) transcended by a substantial factor the doses used in the present study, which have been shown to be sufficient to induce prolonged tolerance in the cat (Adey *et al.* 1962).

Nevertheless, it appears that LSD may act in this respect as a trigger in the removal of modification of a substrate material. This view is supported by the findings of a cross-tolerance to substances not closely related chemically, such as mescaline, LSD and BOL-148 (Balistrieri and Fontinari 1959). A most striking prolongation of perseverant and unrewarding motor behavior followed single doses of LSD in fish (Keller and Umbreit 1956), but disappeared when reserpine was given. It would thus appear that these manipulations with LSD and similar substances may modify metabolic substrates

which, in turn, are essential to the normal EEG patterns accompanying focused attention and discriminative performance. These effects can be sufficiently disruptive to destroy discriminative capability (Adey and Dunlop 1960; Adey *et al.* 1962), but more subtle EEG changes can be detected long after the acute phase of drug action.

The consistent finding of such prolonged effects on theta wave trains accompanying the discriminative performance necessarily confronts the genesis of electrical activity, and its regularization during this task performance. The laminar organization of the hippocampus has suggested some identification of these wave processes with the dendritic trees of the pyramidal cell layer (Green *et al.* 1960). Their origin has been suggested in inhibitory post-synaptic potentials (Andersen *et al.* 1963; Kandel *et al.* 1961).

If the origin of these waves lies in a slowly propagated electrotonic process between the dendrites and the cell body (Green *et al.* 1960), then other, more subtle influences in adjacent tissue may alter the frequency of such a process (Green and Maxwell 1961). There is the further possibility of a modification of the impedance loads offered to electrotonic generators in dendritic structures. This may produce altered frequency patterns in the EEG (Adey *et al.* 1963), and may be suggested to underlie the action of LSD on EEG patterns, which persist beyond the duration of any temporary accumulation of ionic material in an extracellular compartment.

A combined approach to the metabolic modifications induced by such agents as LSD and the electrophysiological concomitants of the behavioral changes which accompany them may offer keys not only to coding of information in the central nervous system, but to the mechanisms underlying its storage (Adey *et al.* 1963).

SUMMARY

The effects of LSD were studied in relation to changes induced in computed averages of epochs of EEG records during a discriminative task performance in a series of six cats repeatedly exposed to LSD over a period of many months. Computed averages were prepared from daily training tests of 20 and 40 trials. LSD (75 μg/kg) was given in single doses by intraperitoneal injection at intervals of not less than 3 weeks.

Computed averages of rhythmic hippocampal wave trains during approach performance showed an increase in amplitude and regularity following LSD, typically in the initial waves immediately following presentation of the situation. This modification was maximal about 4 days after LSD, and decayed to control levels after 5 to 7 days. Similar analyses of records from the posterior pyriform (entorhinal) cortex indicated an increment in the early components of wave trains during discriminative performances, which also reached a maximum 2 to 3 days after LSD. Midbrain reticular activity showed only minor changes on days following LSD, also peaking about 4 days after drug dosage.

These findings indicate persistent electrophysiological effects of LSD beyond the period of acute drug action. However, these changes ran a shorter course than the tolerance to LSD exhibited by man and animals. They showed a differential distribution in different brain regions, with maximal changes in the hippocampus, and smaller effects in the entorhinal cortex and the rostral midbrain reticular formation. Evidence is presented of highly focal differences in late responses within the hippocampus. Differential susceptibility of hippocampal tissue is discussed in relation to a similar sensitivity to the acute effects of both LSD and psychotomimetic cyclohexamines, and to the pattern of propagation of hippocampal afterdischarges.

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