Int. J. Neuropharmacol., 1965, 4, 255–264 Pergamon Press. Printed in Gt. Britain. [7 figs., 18 refs.]

SPECTRUM ANALYSIS OF EEG CHANGES INDUCED BY PSYCHOTOMIMETIC AGENTS*

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Summary—The effects of LSD, mescaline, harmine, phencyclidine, bufotenine, bulbocapnine and Brom-LSD on the resting EEG of multiple brain structures have been studied by spectral analysis methods. All the hallucinogenic compounds tested produced changes in the electrical activity of the amygdaloid complex. Alterations in other structures were also noted but appeared to be drug-specific. It is proposed that the limbic system, especially the amygdaloid complex, is an important site of action of hallucinogens.

INTRODUCTION

PSYCHOTOMIMETIC agents are known to induce behavioral changes in man and experimental animals. Perceptual and affective changes are produced by the hallucinogens; catatonia by bulbocapnine. Their sites and mechanisms of action in the central nervous system are still obscure. This report summarizes the results of our attempts to establish whether or not the electrical activity of certain brain structures is consistently affected functionally by some of these agents. The changes in EEG activity were interpreted as reflecting functional alterations and were quantified by spectral analysis. Our results indicate that functional changes in the rhinencephalon, particularly in the amygdaloid complex, are induced by hallucinogenic agents. This is regarded as a prelude to the application of more refined methods of biochemical and electrical functional analysis.

METHODS

Adult, mongrel cats of both sexes were used. Their weights ranged from 2·5 to 3·5 kg. At least three weeks before the experiments, multiple stainless steel electrodes were implanted in the olfactory bulb, periamygdaloid cortex, basolateral amygdala, dorsal and/or ventral hippocampus, thalamus (anterior complex and/or intralaminar nuclei), caudate nucleus and lateral hypothalamic region. Cortical silver-ball electrodes were placed over the middle suprasylvian or anterior ectosylvian gyri. A steel screw in the frontal sinus or a bare wire looped around the cranium was used as the reference electrode. All placements were verified at the end of the series.

No effort was made to provide visual or auditory isolation from the rest of the laboratory. The animals were placed in a shielded cage and connected to the amplifying and

*Supported by USPHS Grants B–3496 and MH–7997.

†Research Career Development Award K3–NB–15,437, USPHS.

‡Special Fellowship 1 F10 NB–1388–01, USPHS.

recording system via a multilead cable. The electrical activity was amplified by a factor of 6000 or 12000 by RC amplifiers with a bandpass flat between 0·8 and 1000 c/s. It was recorded under visual CRO monitoring by a 7-track FM magnetic tape recorder at a speed of 7·5 in./sec. Each recorded sample, containing a 47-sec epoch, was spliced into an endless belt and run through a spectral energy distribution analyzer (EIDELBERG and CHESHIRE, 1965). The epoch length was determined by convenience for splicing and on the basis of previous observations which indicated the minimum epoch for consistent results was 30 sec. The equivalent bandwidth of the system was constant and close to 1·0 c/s. Sample points were taken at 2 c/s and between 5 and 70 c/s at 5 c/s intervals. The output of the integrating device was plotted in linear units on the ordinates of graphs with the corresponding frequency points on the abscissae. We omitted the numerical values on the ordinates in the illustrations since we were concerned only with changes relative to pre-drug controls.

Each drug was tested on four or more animals and only those changes which were highly consistent among the animals in each group have been included as data. All drugs, in saline solution, were injected intraperitoneally. Control records were taken immediately before injection. The post-drug records shown in the illustrations were taken at the peak of the behavioral effects of the drugs. At least one week elapsed between drug tests in the same animal. The doses used were large so as to obtain maximal changes. No attempts were made to establish dose-response or time-series curves.

RESULTS

Some of the substances tested have been shown to induce hallucinatory behavior in man and/or experimental animals (cf. FREEDMAN, 1963). These include LSD, mescaline, harmine, phencyclidine (SERNYL®) and bufotenine. At the doses indicated in the figures, all induced gross behavioral changes that might be construed as being related to hallucinatory experiences. With the exception of harmine, all caused a marked reduction in the 40 c/s peak in the records from the amygdaloid and periamygdaloid leads, with little or no change in the corresponding records from the olfactory bulb. Harmine caused the appearance, in the amygdala, periamygdaloid cortex and hippocampus, of a large amount of activity in the 20–30 c/s band. This component persisted for several hr but was absent the following day.

In addition to the changes described above, each drug induced relatively specific alterations in the records from structures other than the amygdaloid region (Figs. 1, 3, 4, 5 and 6). The most remarkable change was the appearance of paroxysms of slow wave activity in the caudate nucleus, cortex, amygdala and other structures after LSD, and bursts of spike and slow wave discharges in the caudate nucleus, amygdala, hippocampus and cortex after phencyclidine (Fig. 6). This type of episodic change is not as well demonstrated in spectral analysis graphs as in ordinary inkwriter recordings.

Two drugs tested have been shown not to have hallucinogenic properties (CERLETTI and ROTHLIN, 1955; ISBELL *et al.*, 1959; DE JONG, 1945). Brom-LSD (BOL-148) did not induce any noticeable change in the behavior of our cats at doses up to 1·0 mg/kg, and only caused some increase in the hippocampal slow components and in the olfactory bulb 40 c/s "spindling" (Fig. 2). Bulbocapnine immobilized or reduced motor activity and electrical changes consisting of an increase in diencephalic slow wave components (Fig. 7).

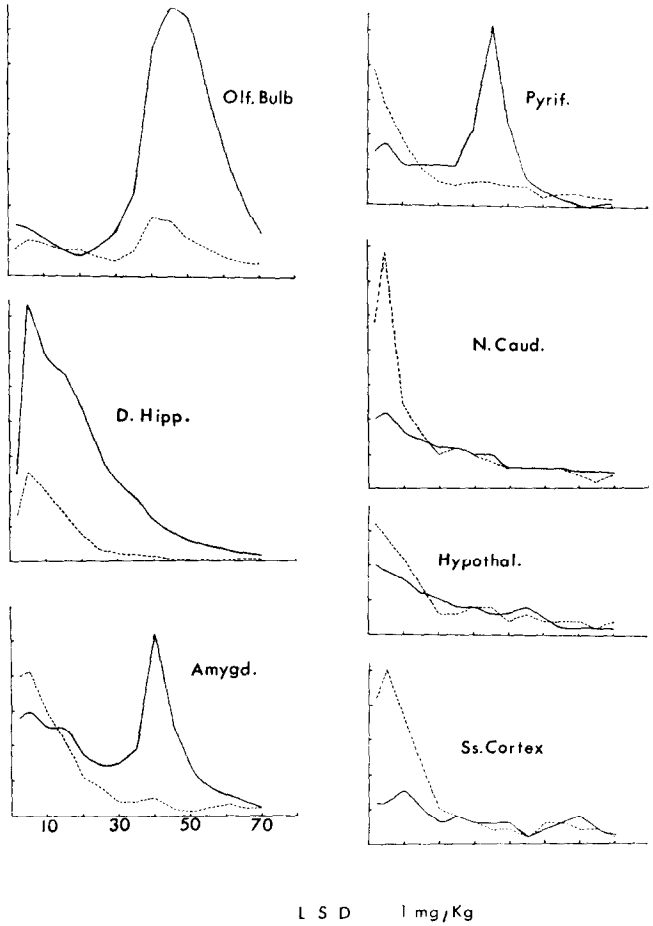

FIG. 1. Energy distribution spectra from several cerebral structures, before and after LSD. Abscissae: frequency in c/s. Ordinates: average energy/second in arbitrary, linear, units. Continuous lines: pre-drug control records. Dashed lines: post-drug records during maximal behavioral effects, 20 sec after its administration.

DISCUSSION

The data presented above clearly indicate that all the hallucinogenic compounds tested caused well defined changes in electrical activity of the amygdaloid complex and the closely related periamygdaloid cortex. It is known that localized changes in these structures can be caused by cocaine, which also possesses hallucinogenic properties (EIDELBERG *et al.*, 1963) and by psilocybin (ADEY *et al.*, 1962). By contrast, a derivative of LSD which possesses no hallucinogenic properties, Brom-LSD (BOL-148), caused no changes in amygdaloid activity. Bulbocapnine, which induces in man a state resembling catatonia without hallucinations, also failed to induce any obvious change in activity in this area. This, plus the ineffectiveness of placebos and of peripheral stimulation in producing comparable changes, suggests that our data are not the result of factors extraneous to the central effects of the drugs.

The immediate conclusion that these hallucinogenic compounds have a common site of action in the amygdaloid region is supported by the work of BALDWIN *et al.* (1959) which indicated that bilateral temporal lobe ablation in primates prevented the appearance of the behavioral effects of LSD.

ADEY and DUNLOP (1960) and ADEY *et al.* (1962) have studied the EEG effects of psilocin, psilocybin, LSD and phencyclidine and have reported that these drugs induce paroxysmal discharges in the hippocampus and elsewhere. They concluded that the hippocampus is the main site of action of these substances and suggested that they act by disrupting the central mechanisms required for perceptual discrimination and memory trace storage. However, our data derived from the experiments with bufotenine, which did not cause any consistent change in the hippocampal activity, would not support that conclusion. These two structures, the amygdaloid complex and the hippocampus, are so closely related functionally that it would be naïve to insist on a strict segregation of effects to one or the other. Also, it is important to emphasize that the conclusion that the hallucinatory process itself is produced by disorganization of limbic function is not warranted by our data. There is evidence to indicate that the hallucinogens are capable

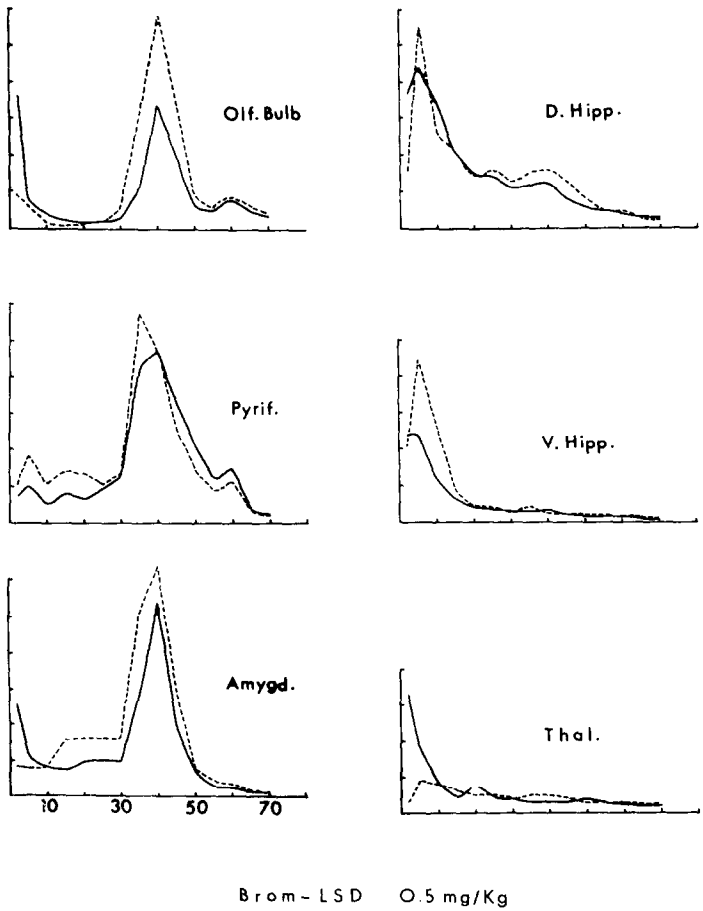

FIG. 2. Effects of Brom-LSD (BOL-148). Same coordinates, etc., as in Fig. 1.

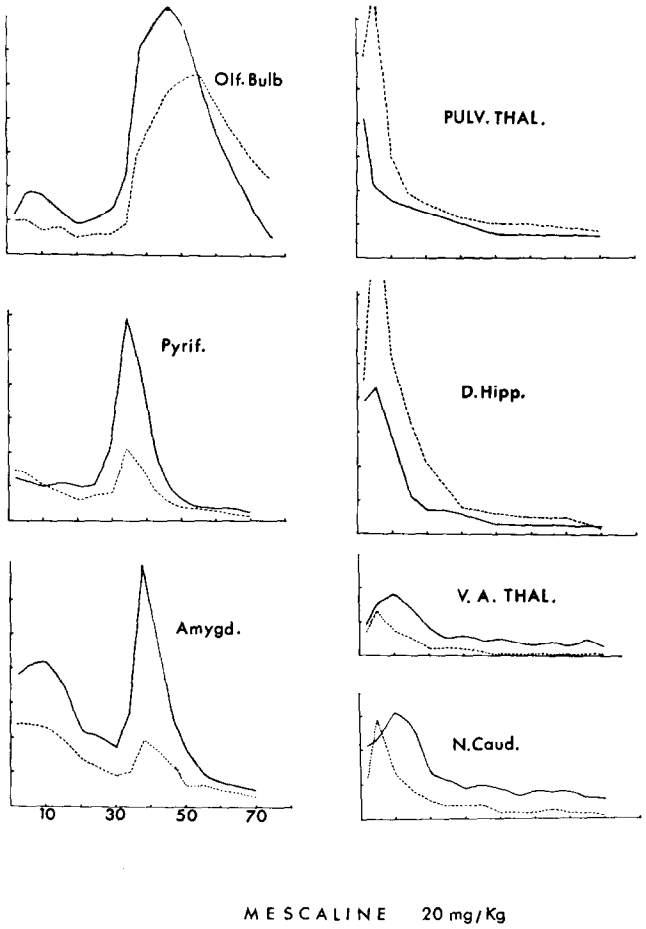

FIG. 3.

of inducing gross functional alterations in the visual system, including the retina (SCHWARTZ and CHENEY, 1965) and lateral geniculate nucleus (EVARTS, 1957). The changes in limbic function reported here may be related more to the development of pathologic behavioral responsiveness to altered visual perception than to alterations of perceptual or discriminative processes *per se*.

A parallel study from our laboratory (in preparation) has led to the conclusion that the electrical activity of the amygdaloid complex can be readily modified by psychoactive compounds which cause changes in brain serotonin levels. The immediate precursor of serotonin (5-hydroxytryptophan, 5-HTP), for example, causes changes in amygdaloid electrical activity which strongly resemble those induced by LSD, mescaline and bufotenine. 5-hydroxytryptophan in large doses causes behavioral alterations resembling those produced by LSD (BOGDANSKI *et al.*, 1958). In our experiments, the electrical changes induced by 5-HTP could be effectively prevented by inhibition of the enzyme transforming it into serotonin. This, plus the finding that several of these hallucinogenic agents cause significant increases in brain serotonin levels (FREEDMAN, 1963; FREEDMAN and GIARMAN, 1963;

UDENFRIEND *et al.*, 1958; HORITA and MCGRATH, 1960), and that serotonin can be N-methylated into bufotenine by tissue (AXELROD, 1962), gives ample support to the proposal by WOOLLEY and SHAW (1954) (cf. also WOOLLEY and CAMPBELL, 1962) that behavior is affected by changes in brain serotonin levels or activity. Our experimental data suggest that rhinencephalic structures, particularly the amygdaloid complex, may constitute key sites for interaction between serotonin and psychoactive agents.

Acknowledgements—The authors wish to express their gratitude to Mrs. P. TOMS, Miss E. WETZLER and Messrs. I. JENKINS, C. GILLIAM, T. JAMES, and F. C. CHESHIRE for their assistance. The drugs used were kindly provided by Sandoz Laboratories (LSD–25 and Brom–LSD), Parke, Davis & Company (Sernyl®) and The Upjohn Laboratories (bufotenine).

Synonyms: Lysergic acid diethylamide (LSD, LSD–25), phencyclidine (Sernyl®, Sernylan®, CI-395); 3–4–5, trimethoxyphenetylamine (mescaline, 7-methoxy-1-methyl-9-pyrid (3,4) indole (harmine, banisterine); 2-Brom-lysergic acid diethylamide (Brom-LSD, BOL–148).

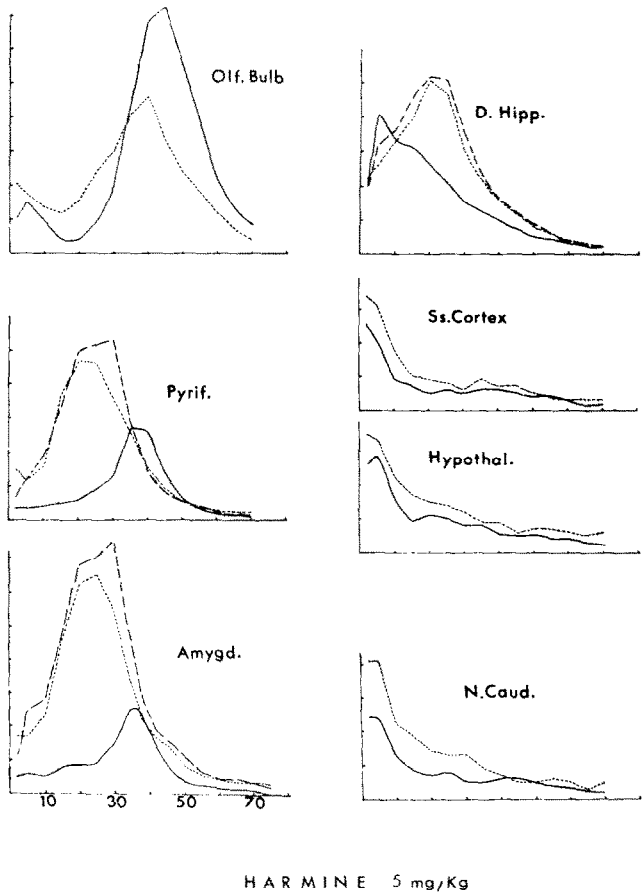

FIG. 4. Effects of harmine. Short-dashed lines: records 30 sec after drug. Long-dashed lines: 4 hr after drug. Both EEG and gross behaviour returned to baseline within 24 hr.

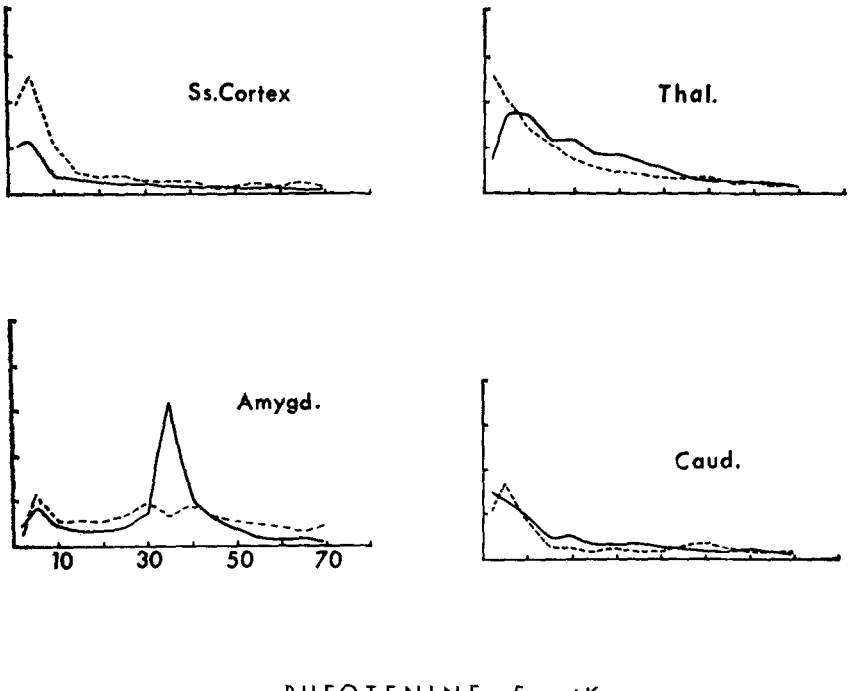

FIG. 5. Effects of bufotenine. Records from periamygdaloid cortex (not shown) closely comparable to those from the amygdala. No consistent changes in hippocampal records. Dashed lines: 30 sec post-drug.

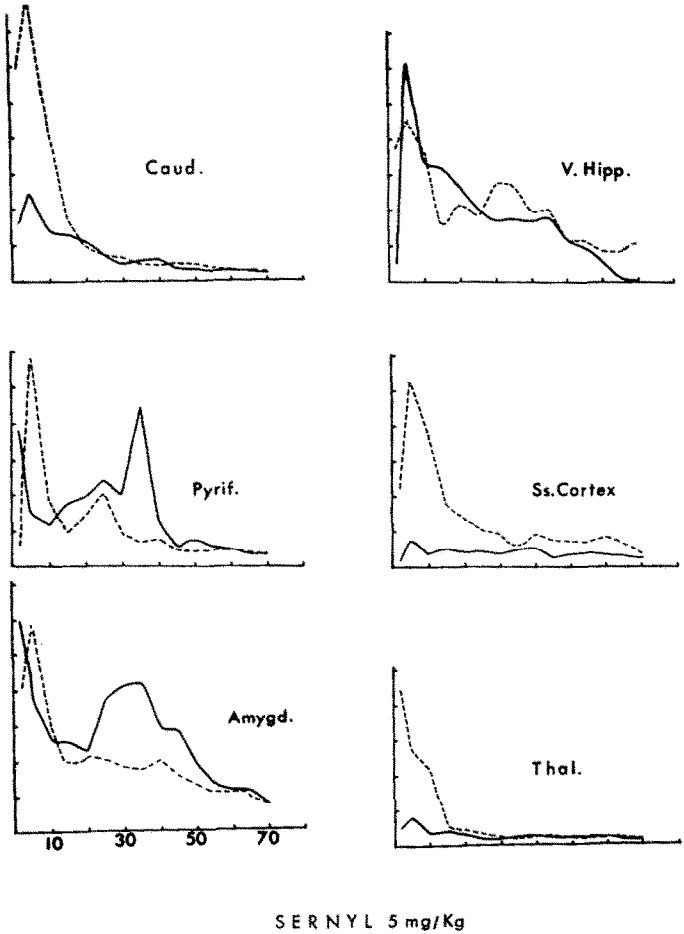

FIG. 6. Phencyclidine (Sernyl) effects. Dashed lines: 30 sec post-drug records.

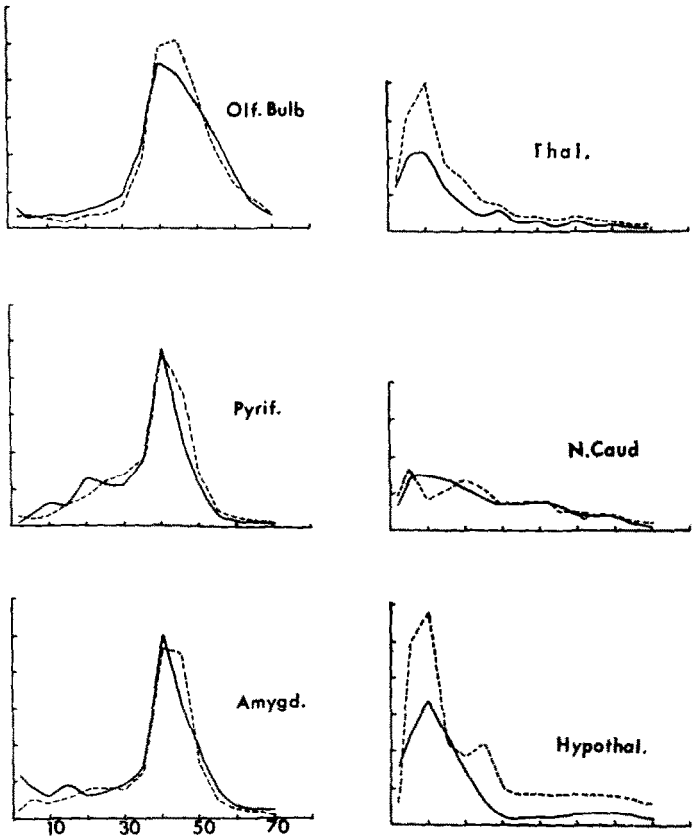

FIG. 7. Effects of bulbocapnine on EEG. No changes in hippocampus. Post-drug records taken 60 sec after injection. Markedly reduced spontaneous motor activity.

Résumé—Les effets de la LSD, de la méscaline, de l'harmine, de la phencyclidine, de la bufoténine, de la bulbocapnine et de la Brom-LSD sur l'EEG des structures multiples du cerveau ont été étudiés par les methodés de l'analyse spectrale. On a constaté que tous les composés hallucinogènes qui étaient mis à l'essai on produit des changements dans l'activité électrique du complexe amygdaloide. Des changements dans d'autres structures ont été également notés, mais ils apparaissaient être spécifiques aux drogues. Il est proposé que le système limbique, surtout le complexe amygdaloide, est un endroit important de l'action des hallucinogènes.

Zusammenfassung—Es wurden die wirkungen von LSD, Harmin, Phencyclidin, Bufotenin, Bulbokapnin und Brom-LSD auf den ruhenden EEG von mehreren Strukturen des Gehirns mittels spektralanalytischen Methoden untersucht. Es wurde gefunden, dass alle gepruften halluzinogenischen Stoffen Veränderungen in der elektrischen Aktivität des Amygdaloidekomplexes bewirkten. Änderungen in anderen Strukturen wurden auch bemerkt, aber sie schienen drogenspezifisch zu sein. Es wird vorgeschlagen dass, das limbische System, besonders das amygdaloidekomplex ein wichtiges Tätigkeitsfeld des halluzinogens ist.

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