

CORRELATION OF RHINENCEPHALIC ELECTROGRAMS WITH BEHAVIOR

A Study on Humans Under the Influence of LSD and Mescaline

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Correlation of behavioral changes with scalp electroencephalograms has been notably unrewarding, although it is difficult to imagine that such behavioral changes could occur without distinct electrophysiologic manifestations in the central nervous system. The development of techniques for implanting cortical and subcortical electrodes in humans has offered a considerable refinement in the experimental procedure of establishing such mind-brain correlations (1, 8, 10). Despite the crudeness of both the instrumentation and manipulation by neurophysiologic standards, some attempts at correlations have already been reported in the literature using the electrode implantation technique (5, 19, 27, 37, 45, 46). Thus, Hodes *et al.* found septal spiking in schizophrenics (24); Sem-Jacobsen *et al.*, high amplitude paroxysmal slow waves correlated with hallucinations (47); and Lesse *et al.*, fast spindling activity with emotionally significant memories (28). Further data on correlations of behavior and brain activity have resulted from subcortical stimulation through these same recording electrodes (4, 5, 6, 18, 20, 31). It seemed reasonable, then, that by inducing behavioral changes with drugs we might have a controlled method of correlating behavioral and brain electrographic activity. Preliminary studies have already verified the usefulness of this method, particularly with the barbiturates, reserpine, chlorpromazine, and alpha chloralose (3, 21, 33, 34, 35).

As d-LSD-25 and mescaline most consistently induce behavioral changes characteristic of psychosis, it seemed that it might be particularly fruitful to study the effect

of these drugs on the depth electrograms despite the lack of consistent scalp electroencephalographic changes reported in the literature. Inasmuch as many behavioral characteristics of the reaction to these drugs are those of an exogenous or toxic psychosis, particularly the distorted perceptual symptoms and illusory phenomena, it is surprising that there is not more cortical involvement revealed by the electroencephalogram. However, the clouding of sensorium and memory loss characteristic of the classic toxic psychosis is lacking, and other symptoms, particularly bodily distortions, feelings of depersonalization, and vague referential paranoid ideas, are more suggestive of early schizophrenia, a disease with a noticeable lack of characteristic scalp electroencephalographic patterns (22, 23). The change, usually induced by these drugs on the scalp electroencephalogram is characterized by the disappearance of the alpha activity apparent in the relaxed record, with the subsequent appearance of beta activity characteristic of tension (41, 42). However, a recent report by Bereel *et al.* (2) suggests that even the scalp recordings may be of more significance than merely reflecting an increase in tension. In his 25 patients, 7 showed an increase rather than a decrease in the alpha index. The beta activity when noted spread slowly from the central (Rolandic) region to other areas, rather than appearing simultaneously throughout the cortex with the disappearance of alpha as one would expect with alertness or tension. Three of their patients showed paroxysmal activity of 6 per sec. bursts in all leads; and 4, paradoxical alpha activity. Delay (7) reported that ex-

tremely high doses in rabbits caused complete flattening of the record with the disappearance of the rhythmic element. A more recent study in animals by Schwarz *et al.* (44) indicates that mescaline placed intraventricularly induces paroxysmal activity in the form of 3 to 4 per sec. sharp waves in the temporal region, as well as longer paroxysms of 10 c/sec. beginning in the right frontal-temporal area, spreading to the occipital region, finally involving the whole hemisphere. Schwarz *et al.* (43) in another study with subcortically implanted electrodes in humans showed that mescaline and LSD induced, particularly from the depths of the temporal lobes and the ventral medial region of the frontal lobes, paroxysmal discharges which consisted of 2 to 7 per sec., spike focus in an epileptic patient, and continuous focal high amplitude slow waves from the ventral medial regions of the frontal lobe during pronounced hallucinations. Generally, these responses were reversed by chlorpromazine. Thus, it seems definite that paroxysmal activity occasionally can be induced on the surface of the cortex and in the isocortex by mescaline and d-LSD-25. The authors felt that extensive subcortical recordings might reveal more consistent electrophysiologic abnormalities than have been found with cortical or scalp recordings.

In this study we recorded not only from isocortex but also from the deeper juxtallo-cortical, allocortical, and diencephalic structures in humans whose behavior was altered by the administration of d-LSD-25 and mescaline, after first establishing careful behavioral and electrographic baselines. The rationale and theoretical considerations which determined the electrode placement have been previously reported (17). As a further check, attempts were made to reverse the behavioral changes by using reputed blocking agents such as Frenquel (alpha-piperidyle-diphenyl carbinol hydrochloride), chlorpromazine, and reserpine. The behavioral changes and electrographic changes were compared with those induced by alpha chloralose, which has already been shown to induce both cortical and subcortical hypersynchronous activity (34, 35).

METHOD

Six patients who had subcortical and cortical electrodes implanted by the stereotaxic method, augmented by ventriculography (1), were used in this study.¹ These were chronically ill patients who had not responded to known therapeutic measures, the subcortical electrodes being implanted for therapeutic purposes, namely, electro-stimulation (17). Table 1 is a summary of the drug experiments. It will be noted that 4 of the 6 patients were unquestionably schizophrenic: one was diagnosed an acute schizophrenic, although there was a question of psychomotor epilepsy, and one suffered from paralysis agitans. Fourteen studies were done with d-LSD-25, ranging in doses from 50 to 200 μ g. There were 9 attempts to block the d-LSD-25 reaction, 6 with Frenquel, one with reserpine, and 2 with chlorpromazine. Two studies were done on 1-LSD-25, 6 with 400 to 500 mg. mescaline either by mouth or intravenously, and 2 attempts were made to block the mescaline reaction, once with Frenquel, another with chlorpromazine. These data were compared with the results of 5 studies on the same patients receiving 500 mg. alpha chloralose plus $\frac{1}{2}$ mg. scopolamine, details of which have been reported before (34). The locations of the intracranial electrodes were as follows: 21 electrodes resting on the pia-arachnoid over the cortex, 19 in the septal region, 26 in the hippocampus and/or amygdaloid region, 9 in the hypothalamus, and 6 in other areas including the caudate, thalamus, nigra and pallidum.

Details of the technique for implantation described elsewhere will not be repeated here (1). Briefly, in the operating room there was a fixation of the stereotaxic instrument to the patient with ventriculograms taken on a superimposed grid corresponding to the two planes of the stereotaxic instrument. Localization of subcortical areas was determined by relationships to bony structures and air in

¹ This was a multidisciplinary research program under the direction of Dr. Robert G. Heath, Chairman of the Department of Psychiatry and Neurology, Tulane University School of Medicine. The program is supported by the Commonwealth Fund.

TABLE I
SUMMARY OF EXPERIMENTS

Patient	Dx	d-LSD (mg.)	+ blocking agent	1-LSD Mesaline (mg.)	+ blocking agent	α chloralose + scopolamine (mg.)	Cortex	Septum	Intracranial Electrodes	Other
							L.Front	R.Ant.	Hippo. Amyg.	Hypo. Caudate
A 11	Schiz. Cat.	100 50 100	Frenquel 50 mg. t.i.d. Frenquel 50 mg. t.i.d.						R.A. Amyg. R.P. Amyg. R.A. Hippo. R.P. Hippo.	
A 12	Schiz. Par.	80 200		400 P.O. 500 P.O.		500 + $\frac{1}{2}$	R&L.F. R&L.Par.	R&L.A. R&L.P.	R&L.A. Amyg. R&L.P. Amyg.	
A 16	Schiz. Heb.	100 100				500 + $\frac{1}{2}$	R&L.F. R&L.Par.	R&L.A. R&L.P.	R&L. Hippo. Ant. Post.	
							*	Left R.A.&P.	R&L. Hippo. R. Amyg.	Caudate, Thalamus
A 19	Schiz. Simple	50 50	Frenquel 20 mg. t.i.d.	100 500 I.V.		500 + $\frac{1}{2}$	L.Front. L.Temp. R.Occip. R.Par.	L.Ant. L.Post.	2 R&L.A. Hippo. 2 R&L.P. Hippo. R. Amyg.	Caudate
A 21	Schiz. Ac. ? Psycho- motor	100	Frenquel 100 mg. I.V.	500 I.V.		500 + $\frac{1}{2}$	R&L.Cor. R.A.&P.T. L.A.&P.T.	R.A.&P. L.A.&P.	R.A.&P. Hippo. L.A.&P. Hippo. R&L. Amyg.	R. Ant. Thalamus
A 22	Paralyses Agitas	100 100	Reserpine 10 mg. I.V. chlorpromazine 50 mg. q.i.d.	1,000 500 I.V.	Frenquel 100 mgm. I.V.	500 + $\frac{1}{2}$	L.Front. L.Par.	Post.	R. Ant. R.Post.	R.A.&P. Thala. R.A.&P. Nigra
		100	chlorpromazine 100 mgm. I.V.	500 I.V.	chlorpromazine 50 mg. q.i.d.					R.A.&P. Caudate L.A.&L.P. Caudate L.A.&L.P. Pallidum
		100	Frenquel 100 mgm. I.V.							
Total 6 patients	14	14	9 blocking	2 1-LSD Mesaline	2 blocking	5 chloralose	21	19	26	9 16

* Two operations with electrode placement.

the ventricles. Placement of the electrodes was checked during the operative procedure and repeatedly throughout the studies. There were no changes in position of these electrodes except for patient A-22. This occurred after the present studies had been completed. The two most significant areas for this particular study were the septal and hippocampal-amygdaloid regions. The septal region has been defined by Heath as follows (16): The caudal border of this area is the anterior commissure; the rostral extent, the tip of the anterior horn of the lateral ventricles. Medially the border is the midline space separating the hemispheres, while dorsally the border is the septum pellucidum proper and the base of the lateral ventricle. Ventrally, the area extends to the base of the brain, and laterally, it extends about 5 mm. from the midline. Thus, it includes in whole or part the subcallosal gyrus, rostrum of the corpus callosum, olfactory tubercle, septal nuclei proper, subcallosal fasciculus, pyriform cortex, and various olfactory pathways. Although physiologically and anatomically the amygdaloid and hippocampal regions are separate entities, because of the difficulties determining in some instances whether electrodes were definitely in the hippocampus rather than in the amygdala, they have been grouped together. The main landmarks used for determining this region were the rostral tip and caudal aspect of the temporal horn of the lateral ventricle.

Following the operative procedure, a period of 2 weeks to one month was allowed for the electroencephalogram to return to the baseline, as the trauma of electrode placement usually induced focal slow wave activity which subsided during this waiting period. All the patients had extensive psychiatric, neurologic, and psychologic work-ups as described elsewhere (17). For extended periods prior to the studies reported here, their behavior was followed closely on the wards, during electrographic recordings, and on visits outside the hospital.

The recordings were made on the standard 8-channel Grass machine using both monopolar and bipolar methods. On some occasions, two

8-channel machines were synchronized to give a 16-channel recording. Both scalp and intracranial electrograms were made in all instances with and without the use of muscle filters. A baseline recording was made before each test, and the recording continued until the drug effect reached its peak. Follow-ups were then made for 15 to 20 min. periods, 4 to 6 hours after the previous recording. On selected occasions, an Offner frequency analyzer was used. This was calibrated with the aid of a standard oscillator and oscilloscope which gave the appropriate Lissajous figures. The drift in analyzer was 0.1 per cent after a 3-hour warm-up. Our machine was stable enough so that weekly calibrations proved sufficient. The patients rested on a comfortable bed in a large, air-conditioned, sound-attenuated room, with all instrumentation and technical assistants in an adjoining room, where a large one-way mirror allowed constant observation of the patient. A 2-way speaker system made it possible to hear spontaneous productions of the patient or to talk to the patient without entering the room. At the time of the baseline recording, a brief mental status examination was done. This was particularly oriented towards determining attitudes about the present study, feelings towards the examiner, basic affect, and immediate ideation, particularly as regards the presence of hallucinations or delusions. Sensorium was checked in some detail. At one-half hour intervals during the experiment the sensorium was re-checked and the patient was asked about subjective changes without resorting to leading questions. The meaning of overt changes in behavior was discussed. During the baseline and at 15 min. intervals after the patient received mescaline or d-LSD, he was told to close his eyes. The examiner pressed lightly on his eyeballs asking what he saw. The flashing lights induced were often perceptually distorted into visual hallucinations. After the experiment was over, the patient was directly questioned about subjective changes, such questions being: "Have you ever had these feelings before? Did the room change in appearance?" etc. Positive responses to these direct questions were eval-

luated carefully as we were well aware of the suggestive element of subjective changes. Behavior was followed closely for the next 24 hours. There was always a period of at least 36 hours between the experiments with different drugs, and in some instances subsequent studies were delayed as long as a week because of the persisting effect of the previous experiment.

RESULTS

Individual responses

A-11. This patient was a 31-year-old mute, manneristic, catatonic schizophrenic who had been psychotic for the previous 10 years.

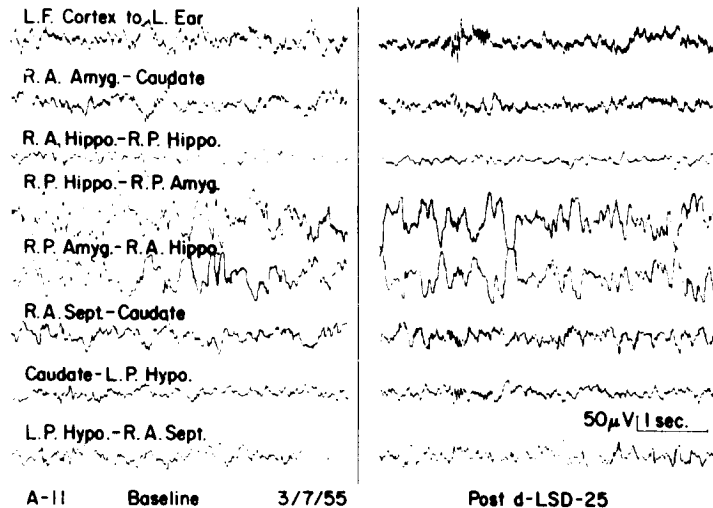


Fig. 1

Increased beta, cortex and caudate following d-LSD-25. Similar change while on Frenquel 50 mg. t.i.d.

Although untidy, he did take care of his personal needs. He had not responded with clinical improvement to EST, Frenquel, reserpine, or chlorpromazine. Since he was inaccessible for the usual psychiatric testing, it was difficult to ascertain what subjective effect, if any, 100 μ g. d-LSD-25 had on this particular patient. The afternoon and evening following the administration of the drug, he was more negativistic, refused to feed himself, and would not cooperate for follow-up studies.

Electrograms showed only a decrease in the small amount of alpha present in the baseline and some increase in the beta activity on the cortex as well as in the caudate area (fig. 1). During a period of 4 hours there were 3 episodes of paroxysmal 6 per sec. waves coming from all leads, with highest amplitudes located in the hippocampal-amygdaloid region. These were of doubtful significance as they occasionally occurred in the baseline recordings. After 19 days' administration of 50 mg. Frenquel three times daily, the response to 100 μ g. of d-LSD-25 seemed to be the same as above described, both behaviorally and electrophysiologically. There were still infre-

quent episodes of paroxysmal activity, but again these were so rare as to be of doubtful significance insofar as having been induced by the drug. As before, the fast activity in the cortex and caudate was noted. Despite Frenquel, he again showed increased negativism the afternoon following the experiment.

A-12. This 27-year-old patient was a paranoid schizophrenic who had withdrawn from all social contact and suspiciously evaded

questions about her underlying delusions of persecution. Periodic anxiety and rage attacks made hospitalization necessary, although patient steadfastly denied that she was mentally ill. Her uncooperativeness made an evaluation of either the d-LSD or mescaline reaction difficult. Despite 200 μ g. of d-LSD-25, the patient showed little clinical change except for minimal somatic sensations such as numbness in the arm. She was more evasive, at times would laugh inappropriately, all of which she occasionally showed spontaneously. There were no discernible changes in the elec-

trograms showed definite changes after the mescaline. Although the response was different on two occasions, so was the baseline which, despite the change within a period of one month, was stable, that is, identical to that shown in figure 2 for at least one week before and after the experiment. In the first instance after mescaline there appeared paroxysmal 10 per sec. activity coming predominantly from the left anterior hippocampal region; while on the other occasion there were episodes lasting for periods up to 20 sec. of high amplitude delta activity in the right

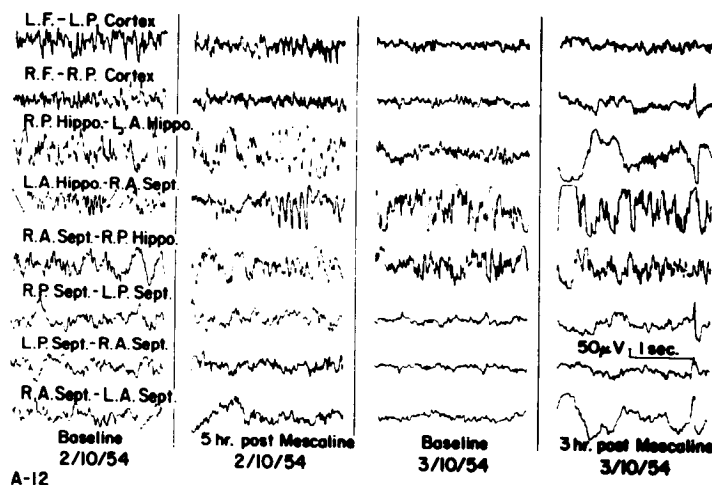


Fig. 2

Different response to mescaline — note difference in baseline. Patient showed no EEG changes with d-LSD-25.

trograms, but there was considerable beta activity present in the baseline cortical electrograms.

This patient received mescaline on 2 occasions. In both instances the behavioral response was more dramatic. She was more open in expressing her hostility and negativism. In comparison to d-LSD-25, she admitted that this drug made her upset even though she refused to describe her subjective feelings. She did admit to a number of somatic complaints such as nausea, numbness, blurred vision, and headache. Once, the nausea was accompanied by vomiting. The

anterior septum, accompanied by sharp high amplitude spikes in the right septal and hippocampal areas reflected also in the right cortex (fig. 2).

A-16. This 33-year-old patient had been psychotic for 10 years. At the time of the present studies, although evasive in certain areas, she was quite loquacious and cooperative, willing to talk about her subjective feelings. Her emotional response was one of bland indifference, inappropriateness, or silly giggling. She was unkempt, dishevelled, rambling, and scattered in her productions. Although not hallucinating, she had a number of bodily

delusions and sexual preoccupations. The behavioral response to d-LSD-25 was dramatic. She said she felt "peculiar", appeared frightened, was extremely restless, writhing in bed as if orgasmic. She would reach out, grab or kiss the doctor, then push the doctor away while expressing numerous guilty and expiatory feelings. At the height of this, she had visual hallucinations of "tombstones on the ceiling". The electrograms at the height of the drug effect showed a sharp 8 to 10 per sec. wave followed by a slow $2\frac{1}{2}$ per sec. component coming from the anterior hypo-

Even more dramatically than in the previous studies high amplitude delta activity in the septal region definitely increased. At other times, in both the septal and hippocampal regions there were high amplitude 6 per sec. flat-topped waves lasting for 20 to 30 sec. Also in the hippocampal leads there would be bursts of sometimes 15 per sec., other times 25 to 30 per sec., activity which occurred in occasional baseline recordings and was presumed to be associated with emotionally charged memories (11). The frequency analyzer revealed a definite shift in all deep

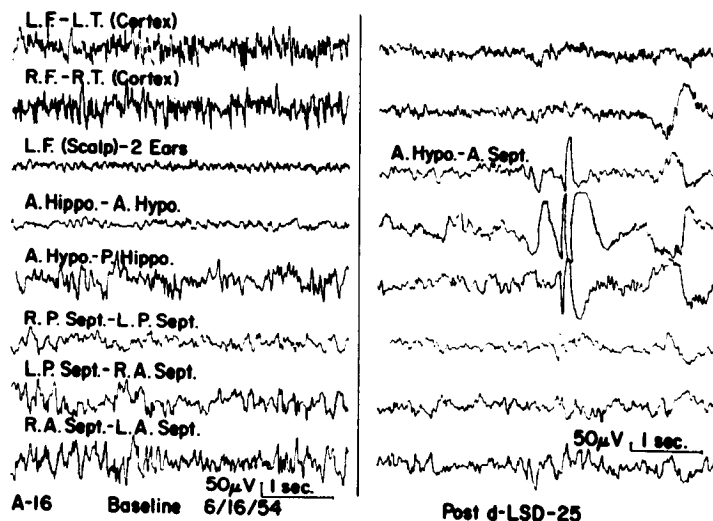


Fig. 3

Sharp wave with slow component from hypothalamus. Spike also occurred in septal region and post. hippocampus. Septal region showed increased delta (not shown in figure).

thalamus (fig. 3), and occasional sharp spikes from the posterior hippocampus and throughout the septal area. At the same time, there was considerably more high amplitude delta background activity in the septal leads. Beta activity present in the cortical leads during the baseline seemed to be definitely increased, although this is not apparent in figure 3.

Nine months later, after a subsequent electrode re-implantation, she underwent a similar study. Although this time she denied hallucinations, her behavior was otherwise similar.

leads to the slower wave frequencies, with 5, 6, and 7 per sec. waves present in the baseline virtually disappearing to be replaced by 1, $1\frac{1}{2}$, and 2 per sec. activity.

At the height of the clinical response, the patient was given 80 mg. of Frenquel intravenously. As she had had amytal on numerous occasions in the past to quiet her down, the suggestive effect of such an injection is obvious. In any event, she immediately relaxed. However, there were only minimal changes on the electrograms. The high amplitude delta

activity in the septal region diminished, but the paroxysmal activity continued even though her behavior was considerably better, there being much less agitation with accompanying hyperventilation. The electrographic changes may have been the result of this rather than the direct effect of Frenquel (fig. 4).

A-19. This 28-year-old patient had simple auditory hallucinations of God talking to him and at times calling him accusatory names which rarely would elicit a rage response with destructiveness. Otherwise, he was emotionally flat and isolated, giving the appearance

increase in beta activity after both drugs, the only difference in the electrograms was the appearance of high amplitude delta activity with the baseline frequency superimposed, appearing in the septal leads. These slow waves were not associated with sleep. The experiment was repeated on a subsequent occasion after the patient had been on 25 mg. Frenquel t.i.d. for a period of 11 days. Although behaviorally the response was very much the same, this time the slow activity in the septal region was not apparent. On neither occasion did the patient admit to hallucina-

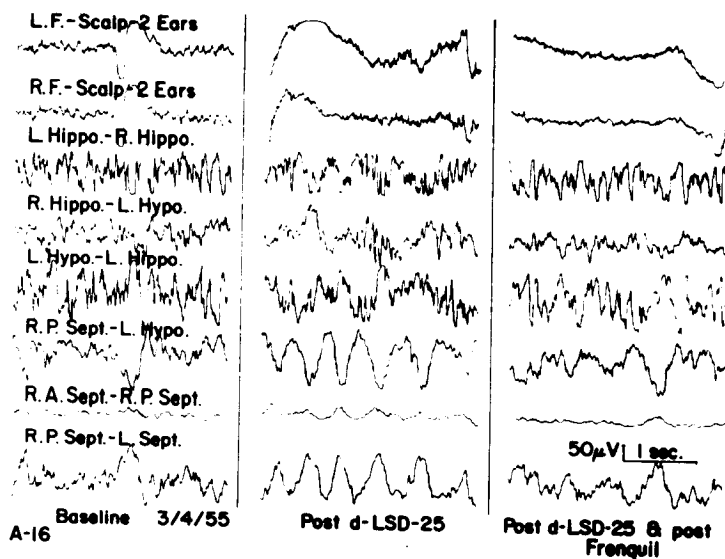


Fig. 4

Slow activity in septum induced by d-LSD-25. Question whether Frenquel responsible for decrease in slow activity.

of a mental defective. He either could not or would not give any detailed subjective data. This patient received relatively low doses of d-LSD-25 (50 µg.). His only comment after the drug was that everything "moved fast", by which he meant that his own actions and those of others seemed particularly quick. He did, in fact, appear overactive and more emotionally responsive than usual. He now smiled broadly, although this was a somewhat sheepish, inappropriate grin. Except for the cortex showing a decrease in alpha with an

increase in beta activity after both drugs, the only difference in the electrograms was the appearance of high amplitude delta activity with the baseline frequency superimposed, appearing in the septal leads. These slow waves were not associated with sleep.

However, following 500 mg. of mescaline intravenously, there was an immediate somatic reaction of blurring of vision, pain in the shoulder and chest, followed one-half hour later by nausea. He also felt that things were "soft", by which he meant dreamy or unreal. With eyeball pressure, the response was as follows: one-half hour, he saw only white lights; one hour, these became red and

blue: at one and one-half hours, he suggested that the yellow colors were flowers and the red were Coke machines; at two hours he saw bones, an airplane, a sword, and apples. On this occasion, the high amplitude delta activity appeared only rarely in the septal region. On the other hand, low amplitude diphasic spikes, sometimes followed by low amplitude slow waves, were noted in the hippocampal region (fig. 5).

A-21. This 28-year-old patient required hospitalization because of episodic rage reactions, during which time she would destroy

occipital headaches. During the intervals between attacks there was demanding, possessive, irritable, and pathologically jealous behavior. At times she was so disorganized that she was unable to care properly for her children or her husband. She had numerous hypochondriacal preoccupations which necessitated frequent trips to the doctor and hospitalization with several laparotomies. On routine scalp electroencephalograms prior to electrode implantation, bi-frontal theta activity was noted but no other abnormality. Baseline deep recordings following electrode implantation

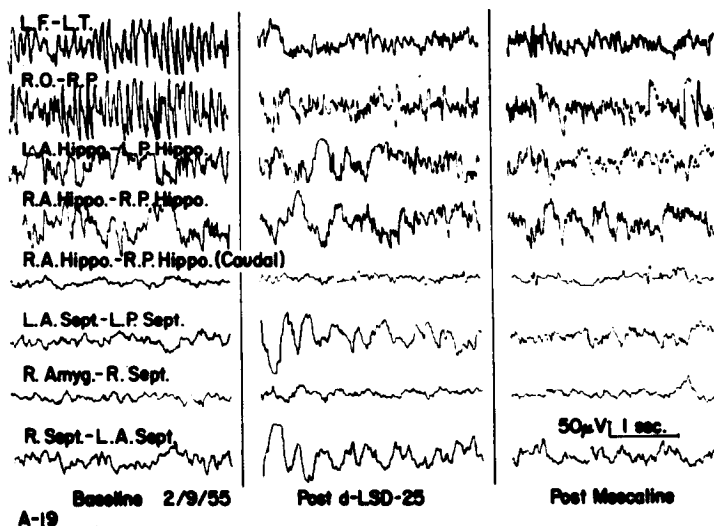


Fig. 5

Slow wave in septum after d-LSD-25 not accompanied by hallucinations. Spiking after mescaline from hippocampus is accompanied by hallucinations.

furniture, attack her husband or children with homicidal intent, and at times mutilate or try to kill herself. During these episodes, she was hallucinating, particularly seeing her children and family, as well as hearing them admonish her for her bad behavior. These episodes were often, but not invariably, accompanied by amnesia, and would last from a few hours to a few weeks, being severe enough to require recurrent hospitalizations where she had in the past been treated with EST. These episodic behavioral disturbances were preceded by mounting irritability and

showed septal theta activity and an occasional diphasic single spike in the left hippocampal region which was never apparent on the temporal cortex except for one instance when the patient had received Metrazol (21).

Figure 6 illustrates the paroxysmal high amplitude bursts of activity in the alpha-theta range appearing in the right hippocampus. The bipolar recording of right anterior hippocampus to right posterior hippocampus showed paroxysms of 6 and 14 per sec. monophasic spikes. Sometimes this paroxysmal activity was seen in the thalamus.

with amplitudes of approximately $5 \mu\text{V}$, as compared to the $200 \mu\text{V}$ recorded from the right posterior hippocampus. Not shown in figure 6, but noticed in the record, was a considerable increase in the sharp diphasic spikes seen during the baseline in the left

in the septal leads in either instance. In this particular patient, then, although paroxysmal activity was induced by both mescaline and d-LSD-25, the latter induced a much more dramatic effect in the electrograms. This correlated well with the behavioral response.

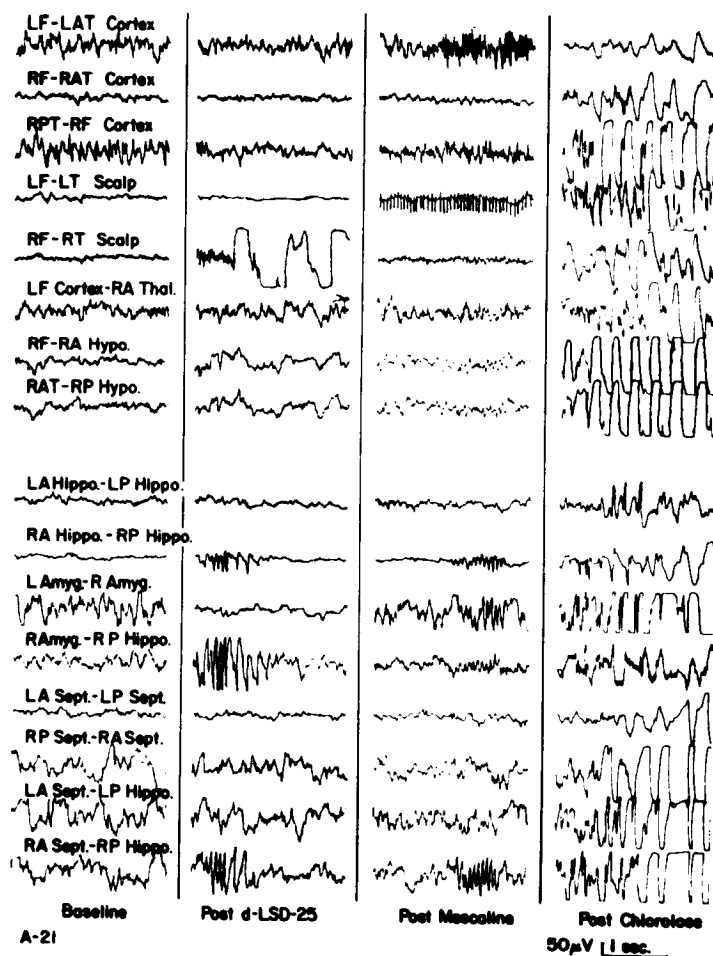


Fig. 6

Paroxysmal activity after d-LSD-25 frequent, but rare after mescaline.

hippocampal leads. With mescaline similar activity was induced in the right posterior hippocampus, but the amplitude was considerably less and the paroxysmal bursts occurred rarely as compared with the d-LSD response. Paroxysmal activity did not occur

Under d-LSD not only did the patient complain of numerous somatic symptoms, such as nausea, blurred vision, head and back ache, but also she became depressed, cried, constantly struggled to get up, and was completely uncooperative. She showed some dif-

difficulty in remembering the doctor's name, appeared to be in a trance-like state, although her attention was easily obtained, and then she was oriented and in good contact with her surroundings. She overtly expressed rage, complained of feeling as if she was going to have a convulsion, mentioned numerous paranoid referential ideas, and hallucinated her children standing at the foot of the bed. On the other hand, after mescaline, although she again had numerous somatic complaints, such as feeling cold, shivering, difficulty in breathing (purely subjective), and reported sensations that her legs were drawing up (also subjective), there was no marked agitation even though she appeared frightened and at times angry. She had a sensation that "everything was pushing in on me", occasionally cried, but this time had no overt visual hallucinations.

Figure 6 also includes electrograms of her response to alpha chloralose and scopolamine. Here the paroxysmal activity is dramatic, with high amplitude delta and theta occurring predominantly on the right but involving bilaterally both the deep and the cortical leads. At other times, sharp spiking activity was the prominent feature appearing in both the right and left hippocampal areas, sometimes synchronously, but often independently. The behavioral response to chloralose was even more dramatic than that with either d-LSD-25 or mescaline. She became agitated, rageful, began tearing up her clothes, and again hallucinated her children and her husband. The hallucinated children appeared frightened and crying, while her husband was admonishing her for her rageful behavior. Under chloralose this patient did not show the extensive cortical slowing that some of the other patients did (see fig. 8 and discussion below).

A-22. This was a 48-year-old colored man of low intelligence with only 2 years' education and an extremely impoverished socioeconomic background. Because of this, an adequate medical history was difficult to obtain. Apparently, 6 months before hospitalization a marked tremor was noted in the right hand for the first time. On admission to the hospital, the tremor included not only the

right hand but the whole right upper extremity with a slight tremor in both legs, all disappearing with activity and sleep. Cog-wheel rigidity was noted in the right wrist. A mask-like facies and slow voluntary movements were present. Other physical, neurologic, and laboratory studies were within normal limits. There was no history of trauma, vascular accident, or infectious disease prior to the onset of the tremor, although 5 to 6 years previously there was a personality change and the patient was no longer able to hold a steady job, was frequently preoccupied, and complained of difficulty in hearing. Routine scalp EEG's prior to electrode implantation showed S2 activity in both frontal leads. There was a slight amplitude asymmetry in the parietals.

When given both d-LSD-25 and mescaline (on separate occasions), the patient became at first more alert and responsive, then confused, agitated, and uncooperative, with a wild frightened look. Whereas before he had been ingratiating, he now would express hostility towards the doctors and technicians. He sat up frequently and talked to himself as if thinking out loud, but did not appear to be hallucinating. He admitted to feeling frightened and asked for medicine to relieve his fear. The same behavioral and electrographic response was elicited on all four studies with d-LSD-25 and two studies with mescaline. One saw first (and most dramatically in the cortical leads) a decrease in the baseline rhythmic activity which in this patient included alpha and theta frequencies, with a subsequent appearance of low amplitude beta. Somewhat later, paroxysmal waves of a frequency of 10 per sec., occurring in bursts of 3 to 6 waves, appeared in the septal leads. Sometimes these would occur singly, appearing like slow spikes. Occasionally a slow spike would appear in the caudate synchronously with this activity. No paroxysmal activity occurred in the thalamus, substantia nigra, or pallidum. This patient did not have electrodes in the hippocampal-amygdaloid region.

The optical isomer of d-LSD-25 (l-LSD-25) is reported to have no clinical effect. Despite the fact that this patient received

1,000 μ g. by mouth, which is 10 times the effective dose of d-LSD-25, no electrographic or behavioral changes were noted.

A number of blocking agents were tried with this patient while he was under the influence of both d-LSD and mescaline. Frenquel, 100 mg. intravenously, did not alter the behavior nor were there any significant changes in the electrograms (see fig. 7). One hundred mg. of chlorpromazine injected intramuscularly at the height of the drug effect of d-LSD-25 did not alter the behavior or the electrograms in the next hour and a half.

theta activity continued throughout the recording (fig. 7), although there were rare periods when this would disappear and the fast beta activity on the cortex and occasional paroxysmal activity in the septal area was seen. On another occasion, at the height of the d-LSD-25 reaction, the patient was given 10 mg. reserpine intravenously. The electrograms were followed for the next hour and a half without significant change. There was no significant change in behavioral response during the next 24 hours as compared to the d-LSD-25 response without reserpine.

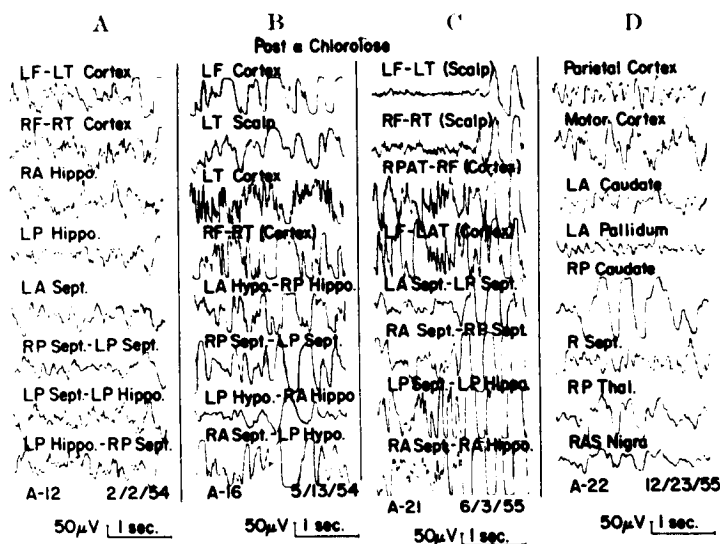


Fig. 8

Response of different patients to chloralose: A — sleepy and relaxed, B — organic confusion, C — hallucinating, D — focal slowing in patient with CNS damage (see text for discussion).

However, early in the afternoon he became quiet and no longer required restraints, which had been necessary during the previous experiment with d-LSD alone, until late in the evening. Because of this delayed effect, he was next placed on chlorpromazine 50 mg., 4 times a day for a period of one week and then tested on d-LSD-25 and mescaline on separate occasions. Although he would appear somewhat restless, the reaction was much less severe than previously encountered. He always remained cooperative. There was a definite difference in the electrograms. The rhythmic

Comparisons between patients

All electrograms, with one possible exception, revealed some response to both d-LSD-25 and mescaline. The generalized response occurred predominantly in the cortical leads; that is, there would be a disappearance of the alpha activity characteristic of the resting record and an increase in the fast activity in the beta range. If there was rhythmic theta activity or underlying delta, this would also decrease in the cortical leads to be replaced by the fast beta. Subcortical activity, particularly from the caudate, amygdaloid-hippocampal,

TABLE II
ELECTROGRAM AND BEHAVIORAL RESPONSE

Patient	d-LSD-25		Mescaline		Blocking Agent		α Chloralose	
	Electrogram	Behavior	Electrogram	Behavior	Electrogram	Behavior	Electrogram	Behavior
A-11	cort. beta no subcort. change except beta	slight increase in negativism			Frenquel no change	did not block drug effect		
A-12	baseline tension no change cort. or subcort.	slight increase in negativism	<i>parox.</i> in septum & hippo.	somatic symptoms open hostility			parox. deep cort. slowing	sleepy
A-16	cort. beta sept. slow <i>parox.</i> sept., hippo., hippo.	agitated, erotic, guilty, hallucinates			Frenquel less slow in the septal region	quiet, coop.	parox. deep cort. slowing	disorientation memory loss, perseveration, amnesia
A-19	cort. beta no change deep	over active	<i>parox.</i> hippo.	somatic symptoms hallucinations	Frenquel no change	did not block drug effect	par. x. deep cort. slowing	relaxed
A-21	cort. beta <i>parox.</i> hippo.	somatic symptoms emotional lability agitation hallucination	cort. beta rare <i>parox.</i> hippo.	somatic symptoms perceptual changes restless	Frenquel no change	did not block drug effect	parox. hippo. no cort. slowing	emotional lability agitation hallucinations
A-22	cort. alpha cort. beta <i>parox.</i> septal	agitated uncoop. talked to self	cort. alpha cort. beta <i>parox.</i> septal	agitated uncoop.	Frenquel no change back to baseline	did not block chlorpromazine behavior back to baseline	parox. rt cort. & caud. reflecting CNS damage, genl. slowing	sleepy relaxed

and septal areas, would often show similar change, that is, a decrease in amplitude and increase in the fast activity. This is similar to the response found by Schwarz (43), that the amplitude of subcortical activity is diminished under the influence of d-LSD and mescaline. Three records were analyzed by an Offner frequency analyzer. This showed that even when fast activity appeared in the subcortical areas, there was a shift in the background activity to the slower frequency bands. A record that might show 5, 6, and 7 per sec. activity before d-LSD-25 or mescaline, would now show more 1, 1½, and 2 per sec. activity.

from background activity, not only because of the wave form, but also because this activity appeared in bursts of one to 10 or more seconds duration. It consisted of the following wave forms and frequencies: 6 to 10 per sec. rhythms lasting for 3 sec., short bursts of high amplitude delta, slow spikes or sharp waves, high amplitude sharp waves followed by a slow component, low amplitude diphasic spikes alone or followed by low amplitude slow component, and monophasic spikes. The wave forms described here were similar to those reported by Hodes *et al.* (18, 24) for schizophrenic patients. All of the schizophrenic

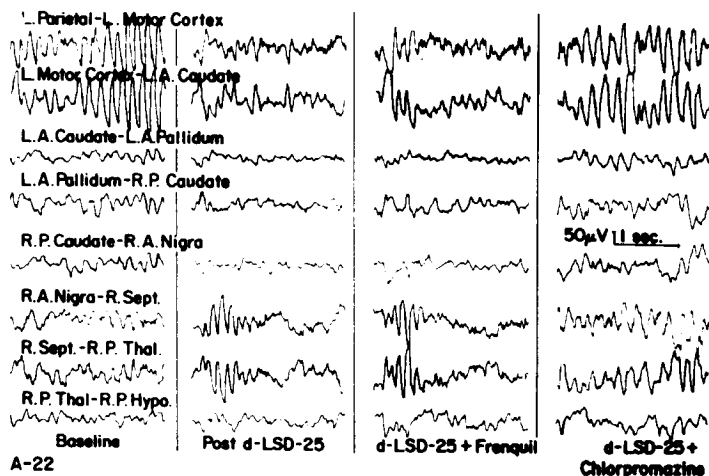


Fig. 7

Decreased cortical alpha and paroxysmal septal activity after d-LSD-25. No change with Frenquel. Return to baseline with chlorpromazine.

This was particularly true of the septal and hippocampal-amygdaloid recordings.

The most significant response to d-LSD and mescaline was the appearance of subcortical paroxysmal activity. This occurred in every patient except A-11, and even in this patient there was suggestive evidence of rare paroxysmal activity. Such activity was most often limited to the septal, anterior hypothalamic, or amygdaloid-hippocampal regions. Table II shows that the paroxysmal activity often did not occur with both drugs. This paroxysmal activity was easily distinguished

patients (patient A-22 the exception) had similar wave forms in their waking and/or sleeping baseline recordings. However, the difference in the recordings when the drug was effective was striking because of the paroxysmal bursts of such activity, the unquestionable increase in amplitude of the waves, as well as an increase in the amount of these waves.

Despite the fact that three of the patients, A-11, A-12, and A-22, were chronically ill people who were either unable or unwilling to be subjective reporters, all 6 patients

definitely showed behavioral changes indicating that the drugs were clinically effective. However, there was a wide range in behavior, from mere anxiety to hallucinating psychoses. In those patients who simply showed a decrease in the rhythmic alpha or theta activity of the cortex and an increase in the beta, the behavioral responses were not marked and seemed indicative of increased tension. Such instances would be patients A-11, A-12, and A-19, under d-LSD-25. However, the latter two did show more dramatic behavioral changes under mescaline with accompanying paroxysmal subcortical electrographic activity.

The converse was true of patient A-21. Although mescaline did induce rare paroxysmal activity, there was a marked contrast between the frequency of these paroxysmal bursts as compared with the response under d-LSD-25 where the paroxysms occurred at 10 sec. intervals. Again there were corresponding differences in behavior. With the d-LSD-25 the patient was considerably disturbed and hallucinated; while under mescaline, although restless, the response was much less dramatic. Patient A-22 showed paroxysmal activity with both drugs, and became equally disturbed on both occasions.

As the more dramatic behavioral changes were also accompanied by somatic symptoms, particularly aches and pains, blurring of vision, dizziness, shivering, nausea and vomiting, one might say that the paroxysmal activity was correlated with the somatic symptoms. This seemed to be true in most instances but would not necessarily preclude the conclusions of the preceding paragraph. In one patient, A-21, the somatic symptoms were equally marked under both mescaline and d-LSD, yet under mescaline, there was minimal paroxysmal activity in the depth electrogram; so that correlation between somatic symptoms and paroxysmal electrograms appears less likely.

We next checked our results by using blocking agents to alter the behavioral response, while noting any corresponding changes in the electrogram. The only blocking agent extensively studied was Frenquel

(alpha-piperdyle-diphenyl carbinol hydrochloride) which was tried in 6 instances on 5 patients under the influence of d-LSD-25 and in one instance on a patient under the influence of mescaline (table I). Unlike the electrographic effects obtained in rabbits by Rinaldi *et al.* (40), we found only questionable electrographic change in our human subjects. This corresponded with the questionable behavioral changes. In most instances, there was no lessening of the d-LSD or mescaline reaction whether Frenquel was given as 100 mg. intravenously during the experiment, or in 20 to 80 mg. doses t.i.d. for several weeks prior to the experiment. In one instance, there was a dramatic clinical response to Frenquel (patient A-16). In view of the lack of response in the other patients, we interpret this change as resulting from suggestion, inasmuch as the patient previously had had frequent intravenous injections of amytal to alleviate her agitation. Figure 4 shows the disappearance of the high amplitude delta activity in the septum after Frenquel. As there was overbreathing during the height of the LSD response, it is questionable whether the disappearance of the high amplitude delta might not be due to the lack of hyperventilation rather than to any direct effect of Frenquel itself. However, one other patient, A-19, without showing behavioral changes, did show less septal slow activity after Frenquel. The only consistent blocking effect was noted with chlorpromazine, although our studies with this drug were limited to 3 experiments on one patient, A-22. Two studies were done after the patient had been receiving chlorpromazine 50 mg. 4 times a day, for a period of at least a week before administration of d-LSD or mescaline. In contrast to the previous studies without chlorpromazine, the patient showed only slight restlessness and occasional lack of cooperation because of his confusion. The electroencephalographic response paralleled this difference in behavior. Figure 7 illustrates the blocking effect of chlorpromazine and contrasts it to the lack of blocking effect, as far as electrograms are concerned, with Frenquel. The EEG response induced by d-LSD and mescaline alone, which has been described

above, occurred only rarely when the patient had been on chlorpromazine.

Ten mg. of reserpine given intravenously on one occasion to patient A-22, with the record followed for the next hour and a half and the behavior for the next 24 hours, showed no effect either on the electrograms or in behavior.

As a further check on whether the paroxysmal activity in the hippocampal-septal region was correlated with psychotic behavior, the findings with d-LSD and mescaline were compared with alpha chloralose studies done on 5 of the 6 patients. These studies have already been reported in a previous communication (34). In summary, it has been found that 500 mg. of alpha chloralose and $\frac{1}{2}$ mg. scopolamine, although used clinically as a sedative, elicits paroxysmal hypersynchronous activity in patients with a history of epilepsy or central nervous system damage. Also, it was found that in many psychiatric patients, particularly those who showed behavioral disturbances in the past, paroxysmal hypersynchronous activity could be induced, and when this occurred there were oftentimes dramatic changes in behavior simulating the spontaneous behavioral disturbances that led to the patient's hospitalization. Consequently, it was felt that if alpha chloralose would induce the paroxysmal changes in the hippocampal and septal region as LSD and mescaline had, and if these were accompanied by similar changes in behavior, it would further support for our thesis that paroxysmal activity in the hippocampal-amygdaloid and septal regions is correlated with psychotic behavior. We found that if, as in patients A-12 and A-19 (table II and fig. 8), the paroxysmal activity was minimal but the generalized slowing predominant, one was most likely to see relaxed, sleepy behavior. However, if generalized paroxysmal high amplitude delta activity was present, such as that shown by patient A-16, the response was more likely an organic confusional state with disorientation, memory loss, perseveration, amnesia, accompanying any manifest disturbance in behavior. On the other hand, if, as the case of patient A-21, high amplitude paroxysmal activity occurred

in the septal-hippocampal region with only slight paroxysmal activity reflected in the cortex and little generalized slowing, the response was similar to, if not even more dramatic than, d-LSD and mescaline. With chloralose and scopolamine this patient showed some slight confusion and slowness in performing simple intellectual tasks, but she never became disoriented. She did become extremely agitated, hallucinated her children, talked with the hallucinations, and struggled to get away from them. The same patient in a repeat chloralose study at a later date showed less deep paroxysmal activity with more generalized slowing in the cortex. At that time she did not hallucinate, was not nearly as agitated, but did become more confused. It would seem, then, that if paroxysmal activity is induced in the septal, hippocampal-amygdaloid region without dramatically affecting the cortex or being accompanied by generalized cortical slowing, the behavioral changes are more marked, while the clouding of sensorium and disorientation is minimal.

DISCUSSION

The important question to ask at this point is whether these findings shed further light on the brain mechanisms in psychotic behavior. Heath (16) points out that the septal region is part of the olfactory system which anatomically would appear to be a correlating structure interposed between the higher neocortical levels and the diencephalic and mid-brain structures. The known connection between the septal region and hippocampus was originally responsible for our interest in subcortical recording from the region of the hippocampus and amygdala. Ablation and stimulation studies on animals imply that these areas are important for such diffuse functions as olfactory-gustatory, metabolic, autonomic, and socio-emotional (38). However, similar studies in humans are infrequent. Heath *et al.* (20) report that in stimulation of the amygdaloid nucleus a rage or fear response is induced without impairment of awareness and that this strong emotional response is conscious as well as integrated into the thinking of the patient. Chapman *et al.*, stimulating the

amygdaloid nucleus in four patients, produced feelings of fear, with only momentary confusions and unresponsiveness, although ability to perform skilled acts seemed to be impaired (6). Others (13) have emphasized the automatism, confusion, and unresponsiveness, with amygdaloid stimulation. Freeman (14) reports that the removal of the amygdaloid nucleus in a psychotic patient with intractable hallucinations led to the cessation of the hallucinations following the procedure. In view of the established anatomical and physiological connections between the temporal lobe and the rhinencephalon (48), studies on temporal lobe epilepsy are pertinent for the problem at hand. It has been noted how frequently automatisms of temporal epilepsy are accompanied by emotional auras, particularly intense fear, as well as the fact that in at least some instances the ictal behavior is not associated with obvious alterations in consciousness (29). Gastaut (15) in his classification of psychomotor epilepsy points out that "hippocampal psychomotor epilepsy" is characterized by obvious interictal clinical manifestations which are marked by character and behavior disturbances. Studies from our own laboratories (11,12) point out the frequency of episodic psychotic behavior in a group of patients with temporal spikes as well as persistent and severe disorganizations of the personality which would suggest a diagnosis of "functional psychosis" in over 80 per cent of the patients studied. The difficulties in differentiating ictal from non-ictal behavior suggest a continuity in the clinical picture probably also reflected by a continuity of the physiologic process. Our present studies on LSD and mescaline suggest that paroxysmal electrophysiologic abnormalities can exist within the rhinencephalon without reflection on the corticograms, hence may be a concomitant of psychotic behavior in many patients now diagnosed as suffering from the so-called "functional" disorders because they lack characteristic seizure abnormalities as recorded by scalp electroencephalogram. In fact, reasoning within the psychoanalytic framework, Menninger (30) suggests that nosologically there is a "third order of path-

ology" standing somewhere between neurosis (second order) and the psychoses (fourth order), which he calls "episodic dyscontrol". These orders represent hierarchically successive groups of control devices that the total organism uses in its adaptation to stress. In this third order there is an episodic "ego failure", variously diagnosed as psychopathic behavior, convulsions, catathymic crises, some schizophrenic reactions, manic attacks, hysterical dissociation, etc. Thus he implies a close relationship between epilepsy, whether grand mal or psychomotor, and some of the now variously diagnosed functional disorders with episodic manifestations such as those mentioned above. It seems to us there is accumulating more and more evidence that paroxysmal activity within the rhinencephalon could very well lead to severely disordered behavior with the adaptive failure so great that such patients are generally considered psychotic. The fact that such behavior showed dynamic content similar to that of dreams (11) and was often more amenable to psychotherapy than pharmacologic treatment has tended to separate this group of disorders from the classic temporal automatism as well as the more complex psychomotor seizures.

The next question one would ask might be as follows: is there evidence from neurophysiologic studies that d-LSD-25 or mescaline does affect the rhinencephalic structures? Although animal studies suggest several subcortical sites of action, a recent study by Killam *et al.* (26) showed that after 50 to 100 μ g. of d-LSD-25 there was little effect on the diffuse thalamo-cortical or the reticular activating system. However, he does report a progressive increase in the duration of rhinencephalic seizures produced by stimulation of the pre-commissural fornix after d-LSD-25. This seems to add some weight to the present thesis that at least in the case of d-LSD-25 paroxysmal activity could be induced in rhinencephalic structures.

Inasmuch as our findings, as well as those of others (43), indicate that chlorpromazine is particularly effective in blocking the d-LSD effect, we might ask the question: is there evidence that chlorpromazine acts on the rhin-

encephalic system? It was found also by Kilham (25) that in cats the thalamic recovery time, though markedly depressed by barbiturates, was unaltered by chlorpromazine. However, with chlorpromazine the arousal patterns within the limbic system were markedly depressed. Thus, the effect of chlorpromazine in blocking the action of d-LSD-25 might be due to this depression of the rhinencephalon, which apparently is, at least electrophysiologically speaking, activated by the action of d-LSD-25.

The above discussion could be criticized on the basis that complex behavioral manifestations should not be ascribed to localized anatomical areas without taking into consideration the inter-relationships between the anatomically diffuse physiologic systems, such as centrencephalic, specific afferent, etc., as well as the rhinencephalic. However, thus far the data from our laboratories reported elsewhere (11, 12, 17, 19, 20, 28, 34, 35) demonstrate that dramatic behavioral changes are usually correlated with electrographic changes in the septal and hippocampal-amygdaloid area rather than the other subcortical areas studied. In a careful study of behavior we must consider the introspective aspects which limit our study to humans. At the same time human studies must be therapeutically oriented, hence variables are often difficult to control experimentally. Many of the more precise neurophysiologic techniques are still inapplicable to human investigation. Because of this, generalizations regarding mind-brain relationship must be made cautiously as guides to further research; but it seems to us that paroxysmal activity, at least in the hippocampal, amygdaloid, and septal areas, is correlated with intense emotions, impulsive acting out, depersonalizations, and at times both perceptual and conceptual distortions which descriptively are considered manifestations of psychotic behavior.

SUMMARY

Six patients with chronically implanted intracranial electrodes were studied under the influence of d-LSD-25, l-LSD-25, mescaline, and correlations attempted between the electrograms and behavioral observations.

An increase in beta activity and a disappearance of alpha characterized in both cortical and subcortical recordings seemed to be associated with anxiety or its derivatives.

Paroxysmal activity induced in the hippocampal, amygdaloid, and septal regions seemed to be associated with overt expressions of disturbed psychotic behavior.

Spread of such paroxysmal activity until it became generalized in the cortex seemed to interfere with the full expression of the psychotic behavior.

Chlorpromazine not only proved an effective blocking agent as far as the behavior was concerned, but also abolished or minimized the appearance of the low amplitude fast activity as well as the paroxysmal subcortical activity. The possible sites of action of LSD-25, mescaline, and chlorpromazine are discussed with reference to the problems of psychomotor epilepsy, episodic psychotic reactions, and schizophrenia.

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