THE INFLUENCES OF THE STANDARD PREFRONTAL LOBOTOMY OPERATION ON HALLUCINATORY PHENOMENA ASSOCIATED WITH PSYCHOTOMIMETIC DRUGS*

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For some years now, we have studied the social, clinical and neurophysiological characteristics of the chronic responsive and therapy-resistant schizophrenic patient. It was speculated that drug responses of patients with a prefrontal lobotomy would help in clarifying the nature of resistance to therapy; therefore, the overall study project included a group of resistant chronic schizophrenic patients who had been treated with a standard prefrontal lobotomy operation. The various groups of patients were subjected to similar clinical and neurophysiological investigations and therapeutic procedures in an attempt to establish specific profiles to differentiate each group. Psychotic patients with overt organic brain disease were also screened as a control group for certain types of investigation. Significant differences in response between chronic lobotomized and non-lobotomized schizophrenics using pentothal and phencyclidine activation techniques [17,18,20] have been reported by us. Differences were also described in sleep patterns [16] and responses to psychotropic drug [12]. Previous reports also described the successful application of symptom provocation techniques using LSD-25 and Ditran in the treatment of therapy-resistant patients [21]. This report describes some of the clinical and neurophysiological findings in groups of patients using the psychotomimetic drugs LSD and Ditran as the investigatory tools. The data will be discussed from the standpoint of the neurophysiological hypotheses concerning the mechanisms of hallucinations.

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Material and Method

1. LSD-25: Thirteen non-lobotomized and thirteen lobotomized schizophrenic patients were selected for this study. The population description is shown in Table I. The mean age for the former was 43 years; and for the latter, 40 years. Diagnostic and psychopathological profiles were similar for the two groups. Matching was also attempted on the basis of length of illness and length of present hospitalization. The mean length of illness was thirteen years for the lobotomized patients. The mean length of present hospitalization for the two groups was eight years and eleven years, respectively. All the lobotomized patients had been operated on at least twelve years previously.

Following a complete routine physical and psychiatric workup, each patient's medication was replaced by placebo capsules; this treatment was maintained for a minimum period of eight weeks. LSD-25 was then given (1 mcg./kg. for females and 2 mcg./kg. for males) intravenously in 5 minutes. The injections were administered in the EEG laboratory under standardized conditions.

Table I. Population Description (Matched Groups of Lobotomized and Non-Lobotomized Schizophrenics) N = 13

Sex:	Male	Female	
	7	6	
Age:	Range	Mean	
Lobotomized	33-51 years	43 years	
Non-Lobotomized	28-49 years	40 years	
Length of Illness:	Range	Mean	
Lobotomized	11-31 years	21 years	
Non-Lobotomized	6-25 years	13 years	
Diagnosis:			
Schizophrenia:	Chronic Undifferentiated		7
	Paranoid		4
	Catatonic		2

EEG eye movement, EKG and EMG were monitored twenty minutes before and for an hour following injection. Each patient was rated on the Missouri Institute of Psychiatry rating scales for psychopathological (70 items) and psychosomatic signs and symptoms (40 items)[19] prior to drug administration and 30 to 40 minutes following the injection. The clinical and neurophysiological data

changes for the two groups were compared using various statistical techniques. The pre- and post-drug EEGs were analyzed visually and quantitatively. For the quantitative analysis of the EEG, power spectral and period analyses were carried out using an IBM 1710 computer.

2. Ditran: Ditran (0.05 mgm/kg. I.V. in 5 minutes) was given to two groups of patients - five lobotomized schizophrenic patients and seven patients with overt organic brain damage. The population description is shown in Table II. The methodology, rating procedures, and analyses were the same as for the LSD-25 study.

Table II. Population Description

Organic Group (N=7)		
Sex:	Male	Female
	4	3
Age:	Range	Mean
	33-62 years	46 years
Length of Illness:	Range	Mean
	3-19 years	9 years
Diagnosis:		
Chronic Brain Syndrome (with M.V.S.)		1
Chronic Brain Syndrome (with pre-senile dementia)		1
Chronic Brain Syndrome (with Korsakoff's syndrome)		1
Chronic Brain Syndrome (with Wernicke's Enceph.)		1
Chronic Brain Syndrome (with mental deficiency)		1
Chronic Brain Syndrome (with cerebral anoxia)		1
Chronic Brain Syndrome (with process schizophrenia)		1
Lobotomized Group (N=5)		
Sex:	Male	Female
	4	1
Age:	Range	Mean
	35-48 years	43 years
Length of Illness:	Range	Mean
	5-29 years	16 years
Diagnosis:		
Chronic Schizophrenia		
Catatonic		1
Chronic Undifferentiated		4

Ditran, 0.05 mgm/kg. given I.V. in 5 minutes.

Results:

1. LSD-25: Psychopathological cluster analysis changes for the non-lobotomized group of patients shown in Table III. An increase in scores occurred in the areas of perceptual disturbance, and disturbances of affect, mood and emotion, communication, consciousness, and higher mental functions. The physical examination also showed notable changes.

Table III. Symptom Changes with LSD-25
Non-Lobotomized group N=13

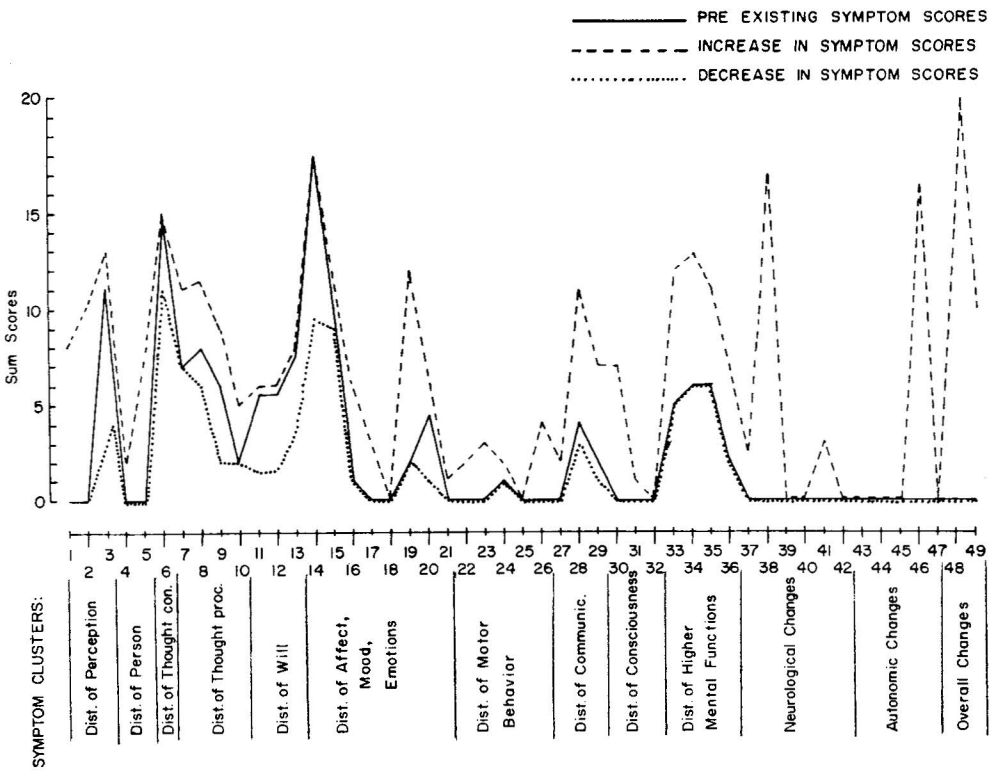
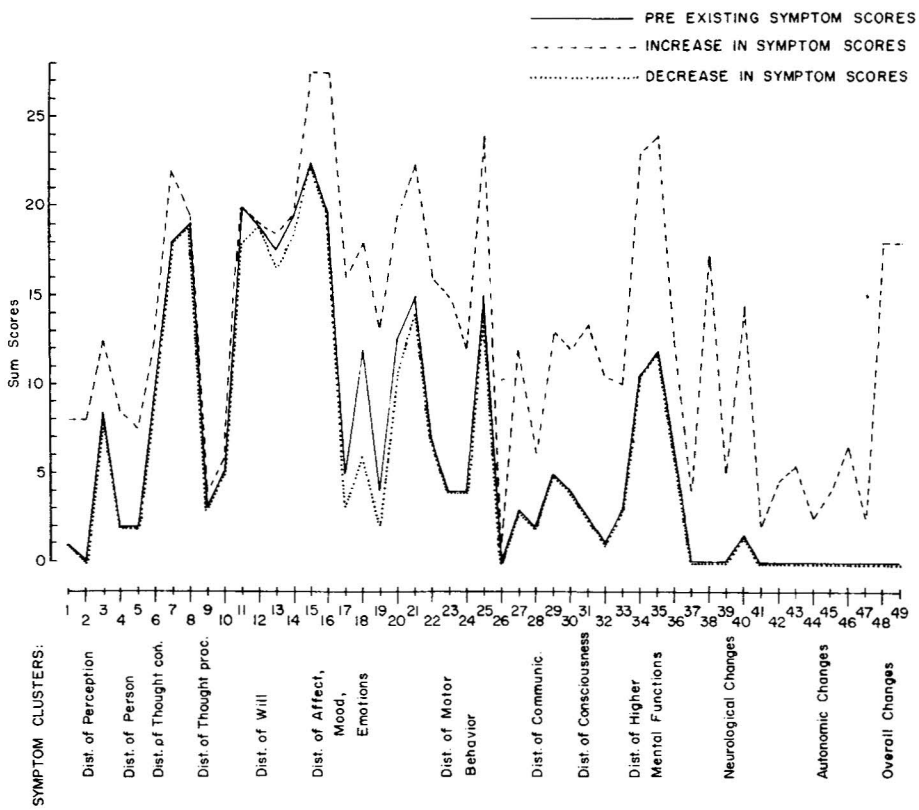


Table IV shows a similar analysis for symptom cluster changes in the lobotomized group of patients. Baseline profiles for psychopathology were more marked for this group of patients, but the changes with LSD-25 administration were even more marked, particularly in the areas of disturbance of perception, affect, mood and emotion, communication, consciousness, and higher mental functions.

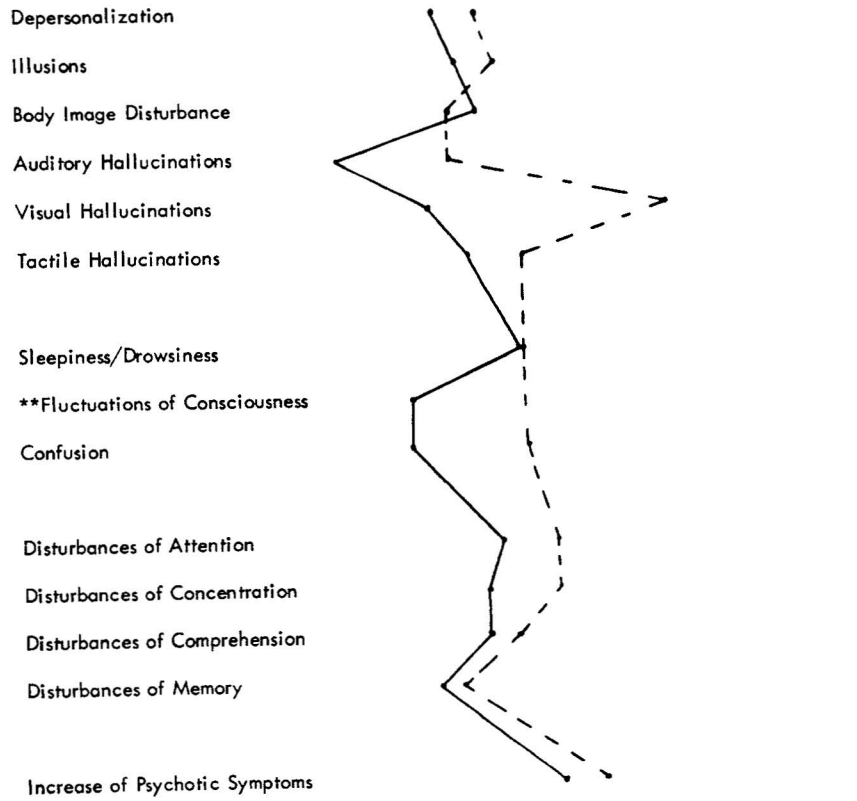
Table IV. Symptom Changes with LSD-25
Lobotomized group N=13



Chi square analysis of individual psychopathological symptoms of the two groups showed statistically significant changes in four items. These were increase of motor behavior (P .05), fluctuation in consciousness (P .05) and disturbance of coordination (P .02) in the lobotomized patients, and a greater increase in pupillary size (P .01) in the non-lobotomized patients.

Table V compares changes in the two groups of patients in selected areas of psychopathology. Apart from body image disturbance, the greatest changes in the lobotomized patients were in visual and tactile hallucinations, consciousness, and higher mental functions. The scores for auditory hallucinations increased in the lobotomized patients, but decreased in the non-lobotomized group.

Table V. Changes in Psychopathology With LSD-25*



* (1 mcg/kg for females; 2 mcg/kg for males, I.V. in 5 min.)

**$P < .05$ (CHI Square Analysis)

Tables VI and VII show the drug-induced EEG changes by patient in the non-lobotomized and the lobotomized groups. After LSD-25, two patients in the non-lobotomized group demonstrated marked EEG changes with decrease in amplitude, decrease of alpha activity, desynchronization, and increase of beta activity. Seven lobotomized patients developed marked changes after LSD-25. Because of patient agitation, some records could not be analyzed quantitatively. Two sample T-tests of the 24 frequency bands of the analog frequency analysis demonstrated significantly more 0-3 cps activity in the

lobotomized group than in the non-lobotomized group before the LSD-25 injection. LSD-25 induced significantly more EEG acceleration in the lobotomized group than in the non-lobotomized group. Alpha activity was significantly less after the injection in the lobotomized than in the non-lobotomized patients.

Table VI. EEG Response to LSD in Non-lobotomized Schizophrenics

Name	Age	Type of Resting EEG Pre LSD-25	Type of EEG Changes 30 Min.post LSD-25 (mcg./kg.)	Degree of EEG Changes
A.P.	35	alpha with theta	slight decrease of alpha, increase of beta, acceleration of background activity, decrease of amplitude	marked
J.T.	44	flat with theta and beta	----------	none
K.D.	28	flat beta with theta	slight decrease of theta	none
E.R.	49	theta with delta and alpha	decrease of theta, increase of beta	slight
R.W.	48	theta with delta and alpha	decrease of theta and delta, increase of alpha synchronization, increase of beta	moderate
L.C.	36	alpha	slight increase of alpha	slight
H.T.	40	alpha	decrease of alpha, desynchronization, flattening, acceleration and increase of beta	marked

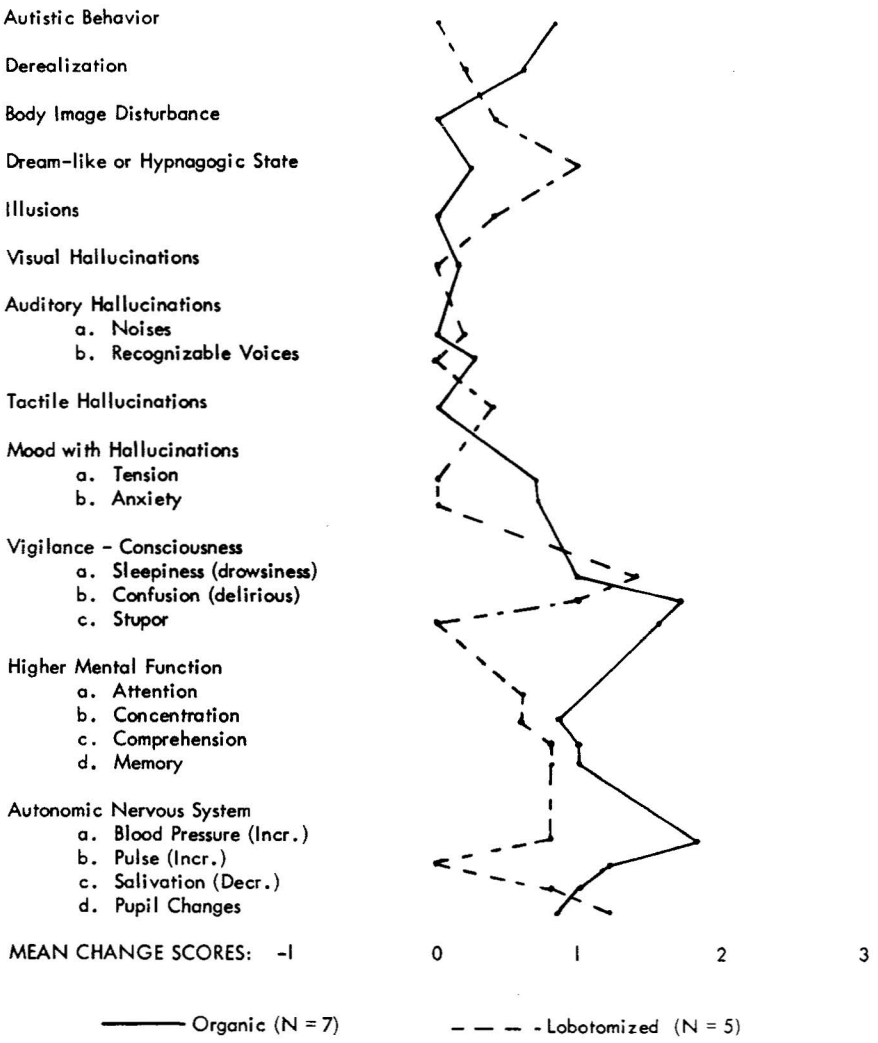
2. Ditran: Some of the clinical changes in the organic and lobotomized patients are shown in Table VIII. A dream-like state occurred more frequently in the lobotomized patients. However, the more striking differences were in autistic behavior, mood, consciousness, higher mental functions, and psychosomatic signs, which were

Table VII. EEG Response to LSD in Lobotomized Schizophrenics

Name	AGE	Type of Resting EEG Pre LSD-25	Type of EEG Changes 30 Min.post LSD-25 (2 mcg./kg.)	Degree of EEG Changes
F.B.	44	alpha	decrease of alpha, desynchronization, flattening, acceleration, increase of beta activity	marked
B.S.	50	mixed alpha and beta frequency labile	increase beta, acceleration of alpha activity, decrease of amplitude	marked
M.M.	49	alpha with synchronization	increase beta, fast spindle activity, acceleration, flattening, desynchronization	marked
J.M.	41	mixed alpha and beta	decrease of alpha, desynchronization, flattening, acceleration, increase of beta	marked
M.K.	40	low voltage beta, mixed with theta and alpha activity	increase beta, slight decrease of alpha, slow theta activity	slight
L.H.	47	alpha	decrease of alpha, desynchronization, flattening, increase of beta	marked
S.H.	33	mixed beta, flat theta and delta	slight decrease of delta	none
T.M.	51	alpha with some synchronization	disappearance of alpha, flattening, increase of beta	marked
T.K.	48	theta with alpha	increase of beta,appearance of alpha, hypersynchronization, sharp waves and single spikes	marked
R.L.	36	delta with theta and alpha	increase of alpha and some beta	moderate
J.G.	35	delta with theta	increase of alpha	moderate
B.D.	40	hypersynchronization,alpha	slight increase of alpha	none

more marked in the organic group. Analysis of the EEG changes in the lobotomized patients showed increases in theta and delta activity, and in frequencies over 20 cps alpha, activity decreased. In the organic patients, striking EEG changes were in delta activity (which doubled in amount) and alpha activity (which decreased). In contrast to the patterns in the lobotomized group, 20 cps activity decreased, but 14-20 cps activity increased.

Table VIII. Changes in Psychopathology with Ditran*



* 0.05 mgm. I.V. in 5 minutes

Discussion

Before discussing the results of this study, I would like to emphasize some aspects of the study structure. First, the clinical ratings were based on verbal evidence provided by the patient as well as overall clinical impressions. All patients were well known to the investigators, reducing subjectivity as a problem in rating. The EEG changes, of course, provide the most objective evidence of differences between the two groups. All EEGs were analyzed at the end of the overall study, and the changes were not known to the clinical rater. Second, when rating hallucinations, the basic definition, "perceptions without corresponding stimuli from without", was applied. Because of basic psychosis and disturbed communication induced by the drug, detailed and reliable descriptions of hallucinatory content could not be obtained in most cases and therefore have not been reported. Third, matching procedures always have their limitations. In this study we attempted to match the groups as closely as possible, but length of illness and hospitalization presented problems. Apropos of this difficulty, one must also take into account the time the lobotomy operation took place, which in this group was 10 to 20 years previously. Fourth, the contrasting neurophysiological effects of LSD-25 at different dosage levels is now well documented. Therefore, one can only accept the results with dosage and mode of drug administration in mind.

Many investigators have reported the effects of LSD-25 on chronic schizophrenic patients, but the results have often been conflicting.[9,10,27,29] In our study there was some increase in overall schizophrenic psychopathology for the group, with corresponding EEG changes. A more significant finding, however, was that the neurological changes induced by the standard lobotomy operation facilitated the development of auditory, visual, and tactile hallucinations and disturbances of consciousness and higher mental function with this drug in the chronic schizophrenic patient. Rinkel described a patient with agitated depression in whom psychosis was reactivated post lobotomy with LSD-25.[28] However, Baldwin felt that there were no significant differences in the reaction of lobotomized chimpanzees to LSD-25 following operation;[4] and Hoch reported a smaller response to mescaline postoperatively in psychotic patients who had been lobotomized.[9] The differences in response found in this study may be attributed to the length of time after operation, which was much longer in our patients.

Various areas of the frontal lobe have rich connections to many subcortical centers.[1] In particular, efferent and afferent pathways link the orbital plate with the anterior and dorsomedial nuclei of the thalamus, hypothalamus, temporal cortex, hippocampus, amygdala, and mammillary bodies with projections to the tegmentum via the mammillo-tegmental tract. Thalamic degeneration or dysfunction after lobotomy in animals and man has been shown pathologically and electroencephalographically.[7,23,26]

These and other neuroanatomical and physiological studies indicate that the orbital cortex is but part of a neurological complex of centers subserving emotional response and probably vigilance and memory to some degree. Our previous studies of activation with pentothal and other drugs provided evidence that the homeostatic integration between the orbital cortex, RAS, thalamus, hippocampus, and amygdala is disturbed by removal of the influence of the orbital cortex and the thalamus.[13,17,18,20]

The excitatory clinical and neurophysiological responses to LSD-25 as reported in this study are consistent with the findings of previous studies.[2,5,8,11,24,25,27] Removal of the influences of the orbital plate would make for instability and disturbed integration between other subcortical centers and therefore an increased susceptibility to LSD-25. The importance of the diencephalon and other subcortical centers in the production of hallucinations was emphasized by DeMorsier.[6] Jackson hypothesized that hallucinations result from the elimination of inhibitory processes.[22] If the LSD effects are based on such release phenomena, the standard lobotomy cut could therefore be anticipated to cause signs of excess excitation.

Another explanation could be based on cortical pathology itself. The standard prefrontal lobotomy operation is frequently associated with gliosis, cystic changes, and cortical atrophy. Schneider described cases in which frontal lobe lesions appeared to have triggered temporal and occipital lobe symptomatology, including auditory and visual hallucinations[30] These influences were supposedly mediated by frontotemporal and frontooccipital association tracts. The presence of frontal lobe pathology and disturbed integration of these pathways could explain the increased tendency to auditory and visual hallucinations in lobotomized patients.

Another mechanism to consider is the relationship between the orbital plate function and reticular formation activity. Specifically, a reciprocal dependence between the orbital plate and reticular formation was recently demonstrated in the rat by Aghajanian et al.[3] Decrease in basal frontal lobe serotonin levels and increase in 5-HIAA occurred with stimulation of the reticular formation at midbrain level with local increase in serotonin. The findings of this and other studies suggest that at least the severity of hallucinations is dependent on homeostatic stability between the orbital plate and reticular formation. It was interesting to note that visual, auditory, and tactile hallucinations increased in this study indicating that the global filtering of sensory imput at the reticular level is affected by cutting off orbital plate influences, with the production and increase of disturbed perception.

The marked consciousness and higher mental function changes could be explained by the LSD effects on the reticular formation--and the limbic system. LSD-25 produces amygdaloid and hippocampal stimulation, which in turn leads to confusion and higher mental function disturbance.[5,24] The elimination of frontal cortical influences and particularly those of the orbital plate could also be expected to lead to excessive reactions in these clinical areas. Many speculations could be made from the findings in this study, but the clinical and associated EEG responses suggest that the frontal lobe cortex or the orbital plate have controlling influences on the responses of the limbic system and/or the reticular formation to drugs. If these influences are impaired, an excessive drug-effect breakthrough via the reticular formation to the limbic system and to the temporal and visual cortex would occur. This approach would be in keeping with Jackson's original theories.

The contrasting effects of LSD and Ditran are also shown in this study. Ditran induced a dream-like state and disturbances of consciousness and higher mental functions in the lobotomized patients. The only changes in perception were the appearance of some tactile hallucinations and body image disturbance. The changes in consciousness and higher mental functions were even more marked in the organic patients. The additional cortical damage in these patients would lessen cortical control even more, as expressed by the marked increase in these symptoms. The Ditran-induced EEG changes of increased delta activity with superimposed fast activity in the patients with organic brain disease are in keeping with the clinical data. According to Itil, et al., Ditran is less likely to produce hallucinations in patients in whom consciousness changes and sleep-like patterns are predominant.[14,15] The greater are the consciousness changes (as shown clinically and electroencephalographically), the less the incidence of hallucinatory phenomena. It has been suggested that the clinical and electroencephalographic effects of Ditran depend on differential changes in the activity of the medial ascending reticular activating system and the medial thalamic diffuse projection system. Activation of the former system by the drug would be associated with cortical inhibition and slow activity in the EEG. If excitatory changes in the latter system predominate, a confusional state and fast activity in the EEG develop.[14,15] The absence of significant differences in hallucinatory changes between the lobotomized and organic patients suggest that the Ditran effect on brain stem systems is so intense that orbital plate influences have little or no effect on drug actions in these areas. The differences in clinical and EEG spectra between the organic and the lobotomized group provide interesting data for further speculation concerning the neurophysiological effects of psychotomimetic drugs. A fuller description of the data and their significance will be described in a further communication.[11]

Finally, this type of study emphasizes the usefulness of combining clinical and objective forms of measurement such as the EEG in any structured research setting where the central effects of drugs are being investigated.

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