LYSERGIC ACID AND ITS EFFECTS ON VISUAL DISCRIMINATION IN MONKEYS

JOAQUIN M. FUSTER, M.D.[1]

The present investigation was undertaken to study the effects of lysergic acid diethylamide (LSD-25) upon the complex behavior of monkeys who were trained to discriminate visual stimuli presented tachistoscopically. This study is an integral part of a more general project designed to correlate some of the behavioral manifestations of visual discrimination with the underlying neurophysiological mechanisms. Earlier results obtained by electrical stimulation of subcortical structures (6) suggested the possible usefulness of the tachistoscopic technique in clarifying some aspects of the action of certain neurotropic drugs. Also, it was felt that the use of drugs conjectured to act upon central systems involved in sensory perception might help to attain the goals of the project. For these reasons LSD-25 was considered to be a good candidate agent for the study. Furthermore, since the phenomenological observation of the transitory effects caused by LSD-25 in man reveals peculiar optic perturbations (13, 14), it was thought that interesting behavioral concomitants of visual discrimination might be manifested by the drug in the subhuman primate.

The neurophysiological aspects of the drug action of LSD have been considered primarily in electrophysiological and biochemical studies. The experimental effects of psychomimetic substances on animal behavior, other than human, are usually either disregarded or unsatisfactorily disclosed, particularly because of the lack of sensitive objective and quantitative methods to carry out their observation. A search for related studies emphasizes the paucity of work utilizing such methods to investigate drug action.

[1] Departments of Psychiatry and Anatomy, University of California School of Medicine, Los Angeles, California. The author wishes to thank Dr. Keith F. Killam for his valuable critical comments on the manuscript. This research has been supported by funds of Grant 2M-6415 from the USPHS.

MATERIAL AND METHOD

Five rhesus monkeys, three males and two females, were trained to discriminate between geometric objects presented in pairs tachistoscopically, *i.e.* in brief exposures. The tachistoscope used as the experimental apparatus is the same as that which has served in other experiments (Figure 1).

The apparatus consists essentially of a one-way vision glass screen separating the animal from the objects utilized as visual cues, and a light source to instantaneously illuminate these objects, which are normally in absolute darkness. A second screen, this one opaque, is normally interposed between the first one and the animal. The training as well as the actual experiments are accomplished by presenting to the animal a pair of stereometric objects, of different shape but similar proportions, in a series of consecutive trials. In this study the objects were a cone and a twelve-sided pyramid, both white. During each session the animal sits in the apparatus, having been adapted beforehand for ten minutes to the semidarkness of the room. For each trial the objects are placed on a black surface on the other side of the screens opposite to the animal. After the opaque screen has been raised and an acoustic warning signal has been sounded, both objects are briefly illuminated for a fraction of a second. The animal has access now to either of the two objects by passing a hand through the corresponding hole at the bottom of the one-way vision screen. These holes are normally

covered by hinged lids. One of the objects (the cone in this investigation) is associated with food by rewarding its selection with a diced piece of apple placed under it before each trial. The position of the correct (rewarded) object, left or right, is changed randomly from trial to trial. The threshold of discrimination, once the task has been learned by the animal, is determined by the proportion of correct responses at each of the various exposure durations. The reaction time, measured from the "on" of the exposure to the moment one of the two doors is opened, is automatically measured.

The exposure duration of 20 milliseconds was selected for the experiment as being close to and above the animal's threshold for the type of visual cues and light intensity (always constant) used. After the animals were trained to discriminate tachistoscopically between the objects, the effects of low concentrating of LSD-25 were tested. Each animal was first submitted to a session of 50 control trials. One hour after the control trials, a dose of LSD-25 was injected I.M., and 15 minutes after the injection, a second series of 50 trials was run. Each session of 50 trials lasted for 25 minutes. The same procedure was repeated one week afterwards with the same animal and the same dose. By this procedure the results on 100 control and 100 experimental (after injection) trials were collected for each animal.

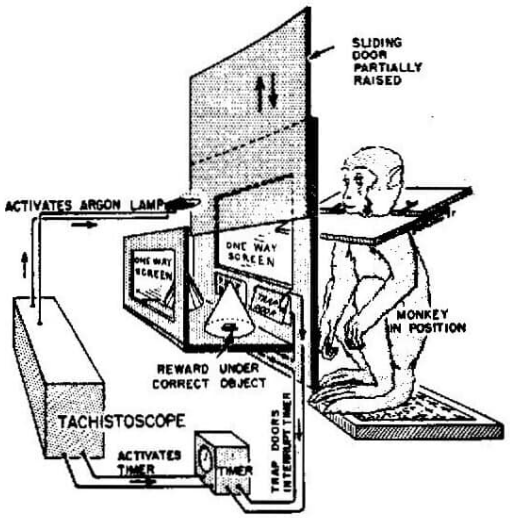

FIG. 1. Diagrammatic view of the tachistoscopic situation. The collar shown around the monkey's neck was used for restraining purposes.

TABLE 1

Compiled Results of Experiment

Subjects	% Correct Responses		Mean Reaction Time in msecs.	
	Control	Drug	Control	Drug
M1	95	75	485	623
M2	97	77	520	614
M3	97	82	545	559
M4	92	78	489	631
M5	90	57	496	644
N = 5 Grand means	94.2	73.8	507	614.2

RESULTS

The administration of LSD-25, at doses between 2 to 8 gamma per Kg. of body weight, proved to impair the performance of tachistoscopic discrimination. The results from the five animals are represented in Table 1 and Figure 2. The effects in the performance[2] are as follows:

1. A significant difference ($p < .001$) was observed in the number of correct responses between the control and the drug series. Accuracy in the drugged state is considerably reduced as compared to the control situation.

2. The difference in the mean reaction times was similarly shown to be significant ($p < .03$). The response time in the discrimination task was prolonged after the administration of the drug.

The impairment of the tachistoscopic performance, in some cases dramatic as indicated by both sets of measurements, was not

[2] A statistical analysis of the data was carried out. Analysis of variance was used on transformed scores of both the correct responses and the reaction times. I am indebted to Dr. Wilfrid Dixon for his aid in the statistical analysis.

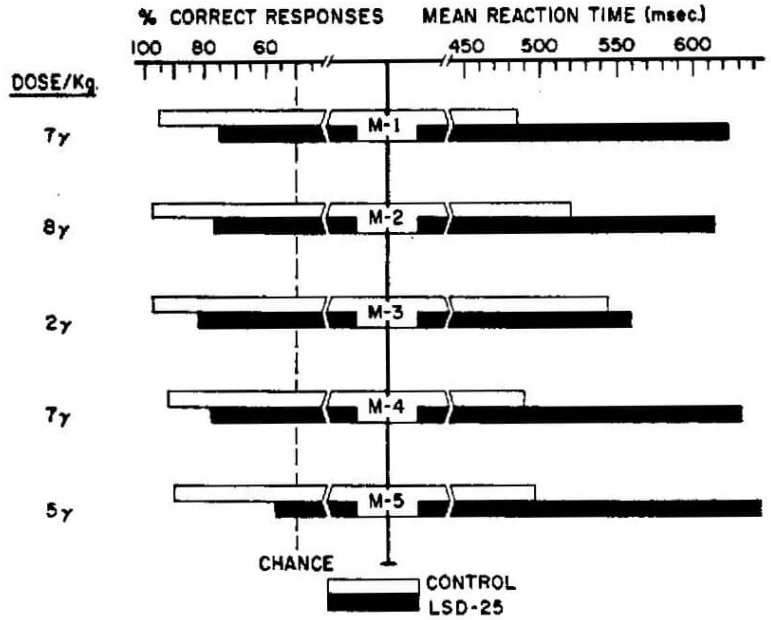

FIG. 2. Graphical representation of the effects of LSD-25 on the tachistoscopic performance

otherwise accompanied by any modification in the apparent behavior of the animals.

DISCUSSION

The results of this investigation indicate that LSD-25 at a low dosage alters the behavior of the animals in the two considered aspects of the experimental situation, *i.e.*, the threshold of tachistoscopic discrimination, which is raised, and the reaction time in the performance, which is prolonged.

From an objective point of view it is difficult to determine from the present study the neural elements participating in the animal performance which are affected by LSD-25. The results, however, are particularly relevant when examined in the light of the body of knowledge on the pharmacology of the drug.

There is electrophysiological evidence at present indicating that LSD affects conduction and/or reception of impulses at various levels in the central nervous system. The sensory pathways and their ganglia have been explored, and among them special interest has been focussed upon the visual system, presumably as a consequence of the phenomenology of the effects exerted by the substance in man.

Interference of lysergic acid with the normal conduction of impulses along the specific visual pathways has been experimentally demonstrated. Evarts and Marshall (5) showed in the cat that the transmission of impulses is hindered by LSD at the level of the lateral geniculate body. This inhibition, interpreted as a consequence of an induced hypoexcitability of the geniculate, is equated by Evarts and Hughes (3) to the state of "physiological subnormality" induced by mild tetanic stimulation of the optic nerve. Evarts and collaborators (4) however, by studying the amplitude of the potentials elicited in the visual cortex by stimulation of the optic radiation fibers, do not find any depressant effect of LSD in the cortex. Yet Purpura (11) has shown enhancement of these evoked potentials in the visual cortex by administration of low doses of LSD to the cat. If this phenomenon is inferred to be correlated with an increase of neuronal excitability and with a concomi-

tant descent of threshold to impulses arriving at the visual cortex, the evidence of impairment in visual discrimination seems to conflict with such as inference. Nevertheless, as we shall see, the cortical effects of the substance appear to be more elaborate.

A selective blocking effect of LSD, as described by Evarts and Marshall, at the level of the geniculate could be responsible for an impairment of visual perception in tachistoscopic performance. However, the effect in the geniculate seems to be a part only of a broader action in the CNS. Purpura (12), citing histological evidence from Glees (7), points out the fact that there is a predominance of axodendritic synapses in the lateral geniculate body. It is because of the particular susceptibility of this type of synapses to the drug, as later discussed, that the effects at the thalamic nucleus can be understood and interpreted.

Marrazi and Hart (10), studying the effects of lysergic acid on evoked transcallosal potentials in the visual cortex, conclude that the drug has a general inhibitory effect upon the synaptic transmission in the brain, in a similar fashion as other hallucinogenic substances whose chemical and pharmacological kinship with adrenaline the authors emphasize.

The importance of synaptic action of lysergic acid has been repeatedly pointed out. Purpura (12) finds evidence for a differential action of LSD on axosomatic and axodendritic synapses. He demonstrates a facilitation upon the former and an inhibition upon the latter. Such effects are observed under quite low doses of LSD to the experimental animals, doses which approximate the ones utilized in the present study and are comparable to those which produce the psychological effects in humans. The distinction between the two types of synapses appears relevant because of the physiological implications of this distinction. Axosomatic synapses are those in which the nervous fiber (axon) contacts the neuron at the level of the cell body, whereas in the case of the axodendritic synapses, the axon terminates by contacting the dendrites of the neuron. The axosomatic type of synapse is characteristic of the connections established by the specific sensory transmitting fibers in the primary sensory areas of the cortex. The axodendritic type is found in the diffuse nonspecific systems of the brain and at the termination of their fibers in the cortex; in this manner the fibers ascending from the diffuse thalamic system and the reticular structures of the mesencephalon establish contact with the cortical neurons. There is considerable evidence indicating that axosomatic synapses are responsible for the electrophysiological transactions that determine the arrival of sensory messages to the receiving pyramidal cells of the cortex, while the level of excitability of these cells to such messages is governed by the electrotonic influences of the nonspecific reticular systems of the brain stem exerted through axodendritic connections (1, 2). These influences, as it is commonly accepted, are responsible for the general state of "arousal" of the cortex, by which, presumably, wakefulness of the organism is obtained and maintained (9). In this connection it is interesting to note that Killam (8) has shown that LSD elevates the threshold of EEG arousal to reticular stimulation.

It is pertinent to consider the results obtained in the present LSD work with those using the same method and under different experimental condition. A current investigation of the effects of electrical stimulation of some structures of the brain (a preliminary report published by Fuster, 6) has yielded data which helps to interpret the role of the nonspecific reticular system of the brain stem. These data indicate that mild electrical stimulation of the reticular core of the mesencephalon tends to facilitate tachistoscopic discrimination. This facilitation is manifested in increments of correct responses and reduction of reaction time; it can be interpreted as the expression of an artificial elevation of reticular tonus, with

a consequent increase of the animal's general alertness. LSD-25, as seen in the present investigation, has opposite effects upon the behavioral indicants. To this extent, the deleterious influence of LSD-25 in the attention-requiring tachistoscopic task is consistent with its postulated inhibitory action upon the axodendritic synapses. For, if reticular tonus is correlated with the degree of general alertness of the organism, an interference with the mechanism by which it is mediated appears to be one of the most probable ways in which the drug disrupts perceptual discrimination. It is not justifiable to propose this as the only action of LSD in the brain, but it can be said that it may certainly be the one which is responsible for the demonstrated elevation of visual threshold and slowness of motor performance as verified by the present study. It appears probable that there are some other concomitant effects of the drug, as suggested by the evidence of axosomatic facilitation which, in addition to the general de-activation previously described, can be the cause of the disorganization of the sensorium demonstrated in humans. It is conceivable that there is a transient activation of some sensory elements (by facilitation of some axosomatic connections), while the general field of external perception is beclouded. The appearance of illusions and hallucinations may be determined this way. The behavioral technique described in this paper is not suitable to test the latter hypothesis.

SUMMARY

Lysergic acid diethylamide (LSD-25) administered to monkeys in small dosage has clear effects on tachistoscopic perception. These effects are verified in the two studied variables: a) the percentage of correct responses in discrimination of briefly presented visual cues, and b) the reaction time to the presentation of these cues. While the percentage of correct responses is lowered, the reaction time is considerably increased by the drug. The effects are proposed to be explained by an inhibitory action of the drug upon the axodendritic synapses of the central nervous system. A LSD-25 inhibition of the cortical terminal synapses of the cerebral reticular structures appears to be corroborated by the results of the present behavioral study.

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