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An Observational Study of Hallucinogen-Induced Behavior in Unrestrained *Macaca mulatta**

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Abstract. An attempt was made to develop an objective behavioral profile that could be used to distinguish the behavioral effects of hallucinogens from those of other classes of drugs. Saline, bromo-lysergic acid diethylamide, and two doses each of lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), chlorpromazine, and d-amphetamine sulphate were administered to solitary adolescent rhesus monkeys whose behavior was observed, videotaped, and scored in a number of categories. Hallucinogens (LSD and DMT) could be distinguished from other drugs by the increased frequency of unusual behaviors such as spasms, stereotypy, and inappropriate behavior, and the decreased amount of exploration time. Hallucinogens also produced distinctive qualitative changes in behavior.

Key words: Hallucinogens — Hallucinations — LSD — Dimethyltryptamine — Chlorpromazine — Amphetamine — Monkey Behavior.

Introduction

A number of investigators have described characteristic behavioral changes in sub-human primates treated with hallucinogens. In monkeys, Klüver (1933) reported that mescaline produced a characteristic "oral syndrome" which was marked by lip, tongue, and jaw movements coupled with licking and chewing. The syndrome was frequently accompanied by "wiping" movements whereby the monkey would wipe, touch, and scratch various parts of its own body. The presence of a similar mescaline-induced oral syndrome in man prompted Klüver (1966) to suggest the possibility of somato-sensory hallucinations (e.g., tactile sensations in the mouth with no apparent stimuli), although he cautioned that observations of such behaviors do not permit reliable inferences about their sensory concomitants. Indeed, Dement and his co-workers (Dement *et al.*, 1970) have argued that the demonstration of drug-induced hallucinations in an animal depends entirely upon what one is willing to infer from the associated behavior of that animal.

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Nonetheless, since the work of Klüver, several studies, albeit lacking objective assessment of such behavioral phenomena as oral syndromes, have indicated that hallucinogens induce dramatic changes in the perceptual-motor behavior of monkeys, if not hallucinations *per se*. Lagutina *et al.* (1964) observed that baboons treated with lysergic acid diethylamide (LSD: 10—40 mcg/kg)[1] exhibited increased orienting responses, hyperexcitability, and periodic catatonia. In addition, the animals grasped at objects in the air, jumped about the cage, and tried to escape "as if frightened". Sharpe *et al.* (1967) found that similar doses of LSD (10—40 mcg/kg) disrupted a visual discrimination task in squirrel monkeys and suggested that LSD facilitated attentional shifts from relevant to irrelevant stimuli. Such irrelevant stimuli could possibly have been internally produced. Borenstein *et al.* (1969) observed similar behavioral changes in *Macaca nemestrina* treated with LSD (100 mgc/kg) and labelled this behavior "visual hallucinatory behaviour". Baldwin *et al.* (1957, 1959) administered LSD (600—800 mcg) to male chimpanzees who were observed to scream, run backwards, beat at the air in front of their faces and above their heads with their hands, and cover their eyes with their hands.

Similar behaviors have been reported when monkeys are treated with delta-9-tetrahydrocannabinol (Δ^9-THC or Δ^1-THC). McIsaac *et al.* (1971) observed marked motor incoordination and jumping, turning, and postural arrest in squirrel monkeys treated with 10 mg/kg. The animals manifested visual gazing which tempted the authors to infer that the monkeys were hallucinating. Numerous other investigators of THC reactions in monkeys have noted "unusual" and "bizarre movements" (Ho *et al.*, 1972); spatial disorientation, circling, and staring; and spontaneous nystagmus with reduced attentiveness to environmental stimuli (Heath, 1973). Such novel and dramatically-described behaviors often overshadow the original experimental design. For example, in studying the effect of Δ^9-THC on operant behavior in squirrel monkeys, Scheckel *et al.* (1968) became more interested in the general behavioral changes exhibited by their subjects. After administration of 4 or 8 mg/kg Δ^9-THC, monkeys sat quietly with head down and peered at the lower part of the experimental chamber. Doses of 16 mg/kg caused the monkeys to "walk about the box, apparently looking at something the experimenters did not see, or to crouch and move their heads from side to side and up and down as if watching some moving object. Some animals had a blank expression and gazed into space [p. 1467]." At higher doses, this behavior became more apparent:

"In some monkeys when the dose of Δ^9-THC was 16 mg/kg, and in all monkeys given 32 or 64 mg/kg, this apparent hallucinatory reaction

[1] The abbreviation mcg is used for microgram.

was more obvious. Monkeys moved quickly about the box, looked above and behind themselves, seemed to be in a state of panic, and appeared to fight with imaginary objects; their arms would swing rapidly through the air and they would attempt to grasp objects that were not there [p. 1467]."

The monkeys also looked intently at their widely opened hands and exhibited postural arrest by holding one or two limbs in an unusual position. These authors acknowledge that some of the behaviors reported such as rapid hand tremors may not have been completely voluntary. Their study fails to provide a carefully controlled study of such observations. Indeed, while hallucinogens such as psilocybin and ketamine have induced related behaviors in monkeys (Bermond and Bert, 1969; Massopust *et al.*, 1972), a wide variety of other drugs such as chloroform, cocaine, and para-chlorophenylalanine (PCPA) have also been reported to produce remarkably similar changes in behavior (Boelkins, 1973; Dement *et al.*, 1970; Deneau *et al.*, 1969; Yanagita *et al.*, 1970).

Therefore, it is not clear (1) what behavioral changes are associated with specific pharmacologic agents, or (2) what is the exact classification of those behavioral changes. As it stands now, based on the purely anecdotal observations in the above studies, the pharmacologic specificity of these behavioral changes is as questionable as the "hallucinatory stimuli" allegedly produced.

The present study was designed to answer these questions with respect to hallucinogen-induced behaviors in unrestrained *Macaca mulatta*. It differs from previous studies in that repeated observations were conducted on individual animals by observers who did not know the drug condition and who had been trained in ethological classifications (cf. Boelkins, 1973; Suomi *et al.*, 1971). Furthermore, a wide variety of psychoactive drugs and dosages were employed.

Methods

Subjects

Subjects were four adolescent (approximately 2 years old) male rhesus monkeys (3.1—4.2 kg in weight) with no previous experimental history. They were housed individually and had free access to Purina monkey chow and water, with daily supplements of fresh fruit.

Drugs

Drugs and dosages were chosen after a review of the literature and preliminary testing on adult rhesus monkeys who were not used as subjects in this study. Two hallucinogens, LSD and dimethyltryptamine (DMT), were chosen. LSD was chosen as a prototypic hallucinogen while DMT was chosen because of its short duration of action allowing for complete assessment of drug effects within a single experimental session (Hoffer and Osmond, 1967; Meldrum and Naquet, 1971; Weil-

Malherbe and Szara, 1971). Bromo-lysergic acid diethylamide (BOL), which has anti-serotonin properties similar to LSD but has no reported hallucinogenic effect in man, was also administered (Hoffer and Osmond, 1967, p. 94). A stimulant, d-amphetamine sulphate (d-A), and a phenothiazine, chlorpromazine (CPZ), which do not normally produce hallucinations in man, were also used (Brown and Bass, 1967; Plotnik and Delgado, 1968; Siegel and Jarvik, in press). Two doses of each drug were administered. The treatments and doses administered were: LSD, 50 and 100 mcg/kg; DMT, 1 and 4 mg/kg; d-A, 2 and 4 mg/kg; CPZ, 0.5 and 1 mg/kg; BOL, 100 mcg/kg; saline. All drugs were administered intramuscularly in a constant volume of 0.1 ml/kg saline. The single exception was BOL which was administered in 0.2 ml/kg saline because of the fixed concentration in ampuls provided by N.I.M.H.

Experimental Apparatus

The experimental observation chamber consisted of a cage (55 cm × 58 cm × 66 cm) similar to the ones in which the monkeys were housed except that the metal front was replaced by a clear Plexiglas door. Food and water were unavailable in the experimental chamber. The cage was illuminated from above by a 40 watt (constant voltage) bulb. Since hallucinogenic effects in humans are reportedly facilitated by a dark environment (Siegel and Jarvik, in press), the light intensity used here was the minimum required to allow for a clear video image. A Sony AV-3210 television camera equipped with an 8.5 mm lens was placed approximately 1 m in front of the Plexiglas door. The cage and camera were enclosed in a sound and light attenuated chamber (Industrial Acoustics Co., Model 1202-A).

The camera was connected to a video monitor and cassette recorder located outside the chamber. Observers, also located outside the experimental chamber, scored behavior using a keyboard (cf. Boelkins, 1973) having 14 buttons, each labelled with one of the behaviors described below. Each time one of the buttons was depressed, a count was recorded on a correspondingly labelled digital counter located on an adjacent relay rack. The keyboard also contained two switches which activated timers for recording the durations (in 0.01 sec) of inappropriate and exploration behaviors (described below).

Behavioral Scoring Categories

The classification of primate behaviors used here was chosen after review of the literature (Boelkins, 1973; Erwin *et al.*, 1973; Hall and Devore, 1965; Hinde and Rowell, 1962; Jensen *et al.*, 1971; Mason, 1960; Mitchell, 1972; Redmond *et al.*, 1973; Rowell and Hinde, 1962; Suomi *et al.*, 1971) and preliminary observations of monkeys under the influence of the drugs to be used in this study. The behavioral categories used by Suomi *et al.* (1971) were judged to be most appropriate for the present study because they had been used in observing single rhesus monkeys in a laboratory setting. The final categories used were:

Locomotion: moving the whole body from one place to another in the cage; changing position from sitting to standing or lying down.

Exploration: visual, tactile, or oral examination of the environment.

Inappropriate: any unusual behavior not often seen by our observers in normal rhesus monkeys.

Stereotypy: movements other than rocking that are performed repeatedly and continuously.

Yawn: yawning; opening and closing the mouth.

Vocalization: sounds or calls; lip-smacking. A number of behaviors involving mouth movements such as chewing and teeth grinding (gnashing) can also be classified as stereotypy. However, such behaviors as the latter are classified here as vocalizations because of their occurrence with lip-smacking and other "oral" behaviors and calls associated with states of fear and excitation (Hinde and Rowell, 1962).

Spasm: convulsive jerking of most of the body; "wet-dog shakes".

Rocking: repetitive forward and backward or side-to-side movement of the body.

Groom: picking or pulling at the skin or hair; cleaning the finger or toe nails.

Self-clasp: clasping any part of the body; huddling with the arms wrapped around the body.

Self-bite: biting or mouthing of any part of the body, usually occurring as a component of grooming.

Fear grimace: executing a fear response with lips pulled back to expose the teeth, sometimes accompanied by turning the head to the side.

Threat: executing a threat response with ears pulled back, eyes wide open, and head thrust forward, sometimes accompanied by quick forward movements of the whole body.

Tracking: following with the eyes and/or hands an object which is not visible to the observer.

The above behaviors were scored by frequency of occurrence. Two time measures were also obtained:

Inappropriate clock: the duration of prolonged inappropriate behavior. This most often consisted of lying prone on the floor of the cage.

Exploration clock: the duration of continued active exploration of the environment.

Experimental Procedure

Subjects (*S*s) were adapted to the experimental cage for 60 min each day. During this period, *S*s' behavior was observed and scored by two independent observers. Differences between the two sets of observer scores were arbitrated and, by the end of the adaptation period, correlation coefficients (Pearson r) between the two observers' scores were 0.93 for the frequency scores and 0.98 for the clock scores.

After six weeks of daily adaptation, drug administration was begun. Saline was the first treatment administered to all *S*s. After this, the nine drug doses were administered in a different random order to each *S*. Each *S* received only one drug treatment per week, with regular adaptation sessions intervening between drug sessions. Only one *S* was treated on any given day.

Drug sessions were conducted as follows: *S* was placed in the cage, a timer was started, and his behavior was observed for a 15 min adaptation period. The videocassette recorder was then turned on for 15 min, after which an experimenter entered the chamber, administered the drug to *S*, and then exited from the chamber. *S*'s behavior was subsequently observed and recorded for 60 min. After the session, two observers without knowledge of the treatment independently viewed the videotapes and scored the occurrence of the above-listed behaviors during the 15 min preceding (pre-drug baseline) and the 60 min following drug administration. The 60 min post-drug period was divided into four blocks of 15 min each and each block was scored separately.

Results

Each behavioral category was analyzed separately. A one-way analysis of variance was performed on the pre-drug baseline scores. Of the 16 behaviors analyzed, a significant difference among the 10 different treatment days was found only on the spasm measure ($df = {}^{9}/_{27}$ $P < 0.05$). Scores obtained after the administration of saline were compared with those from no-injection adaptation sessions recorded before the series of drug injections began. There were no significant or noticeable differences between these sessions except that significantly more grooming occurred after saline administration than during the no-injection sessions ($t = 5.97$, $df = 3$, $P < 0.05$). This increase was probably due to grooming of the injection site. Because of this difference, and lack of changes in pre-drug baseline measures throughout the experiment, saline administration scores were used as baseline controls in all further comparisons of drug effects. For purposes of the analysis of variance, a square root transformation was performed on the data to reduce the large variance (Winer, 1962, p. 220). A two-way (drug $\times$ time) analysis of variance for repeated measures was performed on the data for each behavioral measure. Only drug effects are of interest here and will be discussed in the present paper.

Fig. 1 presents the mean number of occurrences of each activity-related behavior and clock times (in seconds) for each drug dosage, averaged across all subjects and time periods. Only selected behaviors which show good quantitative variation and large drug effects are included here. The data for the remaining measures are presented in Table 1. The measures which showed significant drug effects in the analysis of variance ($df = {}^{9}/_{27}$, $P < 0.05$) are marked with an asterisk (*) in both Table 1 and Fig. 1.

Locomotion was reduced, compared to saline, by all drugs except DMT (Fig. 1). Exploration behaviors (mostly visual orienting responses) were increased by d-A and DMT and decreased by CPZ. Exploration time was decreased by all doses of the hallucinogens LSD and DMT. The only drug which produced more exploration time than saline was 4 mg/kg d-A. The hallucinogens were associated with more inappropriate behavior than the other drugs, although CPZ also increased the amount of inappropriate behavior, relative to saline. High scores in the inappropriate category were obtained by some *S*s after administration of hallucinogens when they repeatedly sat up and laid down in an agitated manner. One *S* obtained a high score for inappropriate behavior after administration of 4 mg/kg DMT when he moved his hands in an unusual manner over the floor of the cage. On the inappropriate clock measure (Fig. 1), hallucinogens produced the largest scores, followed by

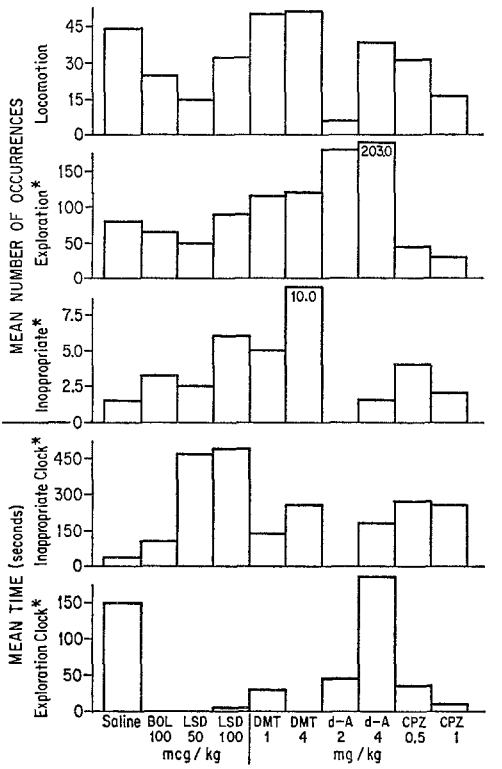

Fig. 1. Mean number of occurrences of each activity-related behavior and clock time (in seconds) for each drug dosage, averaged across all subjects ($n=4$) and time periods. Asterisks denote measures having significant drug effects in the analyses of variance

CPZ. The inappropriate clock was turned on most often when *S* was lying prone on the cage floor. Other behaviors produced by the hallucinogens and timed on this clock were: moving backwards in a circle while sitting down with legs outstretched; sitting with legs outstretched while repeatedly jerking backwards; lying supine on cage floor; moving about the cage bipedally with quick, erratic movements, sometimes backwards, spinning and bumping into cage walls with eyes closed much of the time and tail wagging independently. One *S* repeatedly chased his tail following saline treatment.

In the remaining measures shown in Table 1, stereotypy was produced only after administration of hallucinogens and 4 mg/kg d-A. Some examples of stereotypic behavior that was observed after the administration of hallucinogens were: repeatedly moving hands over cage floor and moving head in a large circle; repeatedly and spasmodically

Table 1. Mean behavior scores for all subjects for each drug condition. Asterisks denote measures having significant drug effects in the analysis of variance

Behavior	Saline	LSD 50 mcg/kg	LSD 100 mcg/kg	BOL 100 mcg/kg	DMT 1 mg/kg	DMT 4 mg/kg	Amphetamine 2 mg/kg	Amphetamine 4 mg/kg	CPZ 0.5 mg/kg	CPZ 1 mg/kg
Stereotypy	0.0	6.7	2.8	0.2	0.0	23.1	0.0	9.5	0.0	0.0
Yawn	0.6	0.4	1.5	0.0	1.1	0.7	0.0	1.0	0.1	0.4
Vocalization*	13.1	2.8	3.2	2.5	4.3	2.6	0.1	46.9	0.7	2.3
Spasm*	0.9	13.1	29.3	2.6	3.4	7.3	0.1	15.9	0.1	0.7
Rocking*	0.0	0.0	5.1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
Groom*	13.9	5.0	2.1	3.8	10.8	6.3	5.2	4.3	5.1	5.2
Self-clasp*	1.5	0.4	0.1	4.1	0.6	0.5	0.0	0.0	3.8	2.6
Self-bite*	4.0	0.0	0.0	0.4	0.4	0.0	0.1	0.8	0.2	0.1
Fear grimace	0.0	0.5	1.9	0.3	0.0	0.1	0.0	0.1	0.0	0.0
Threat	5.7	0.4	0.0	0.4	0.3	0.1	28.2	1.6	0.3	0.2
Tracking	0.3	0.4	1.7	0.6	1.2	8.7	0.5	2.8	0.0	0.0

pulling body against back of cage; repeatedly rocking backward, losing balance, and recovering balance with hand; repeatedly moving hand in an arc over floor in front of prone body. Yawning occurred more often after the administration of hallucinogens than after other drugs. Vocalizations were reduced by most drugs. The only drug treatment that produced a higher number of vocalizations than saline was 4 mg/kg d-A. More spasms occurred after the administration of hallucinogens than after other drugs, except that the higher dose of d-A produced a large number of spasms. The high mean number of spasms after d-A was the result of a high spasm score for one *S*, while increases after hallucinogen administration occurred in all *S*s. Spasms induced by hallucinogens appeared to include convulsive whole-body jerks while those appearing following other drugs resembled head-shakes or "wet-dog shakes". Rocking rarely occurred and the only significant amount of rocking occurred after the administration of 100 mcg/kg LSD.

From Table 1 it is also clear that the administration of all drugs reduced the frequency of grooming when compared to saline. High grooming scores in the first 15 min post-drug period occurred due to grooming of the injection site. The hallucinogens and d-A reduced the frequency of self-clasping compared to that of saline, while CPZ increased it. All drugs reduced the frequency of self-biting compared to saline. Fear grimaces rarely occurred, except after the administration of 100 mcg/kg LSD. Few threat responses were observed, except after the administration of 2 mg/kg d-A when one *S* repeatedly and stereotypically threatened toward the video camera. Tracking occurred more often after the administration of the hallucinogens and d-A than after the other drugs. Tracking usually consisted of reaching into the air or executing a complex chain of visual orienting responses in the air. Two *S*s moved their hands over the floor of the cage in complex patterns, accompanied by head and eye following of the hands. This behavior occurred in one *S* after the administration of 100 mcg/kg LSD and after the administration of 4 mg/kg DMT in the other *S*. One *S*, after receiving 1 mg/kg DMT, executed coordinated eye—hand movements several times, as if following an object in the air, but his eyes were closed.

Discussion

The present results indicate that there were significant overall drug-induced changes in the behavior of unrestrained *Macaca mulatta* when evaluated according to an analysis of behavioral postures. Significant changes were observed in the behavioral categories of exploration (both frequency and duration), inappropriate (both frequency and duration), vocalization, spasm, rocking, grooming, self-clasp, and self-bite. No

statistically significant overall drug effects were found in the categories of locomotion, stereotypy, yawning, fear grimace, threat, or tracking.

Generally, the hallucinogens LSD and DMT, when compared to saline treatment, were associated with increases in the frequency of yawning, stereotypy, spasms, rocking, fear grimaces, and tracking, as well as both frequency and duration of inappropriate behavior. The hallucinogens decreased self-clasping, vocalization, and exploration time. Chlorpromazine was associated with decreases in locomotion, exploration, vocalization, grooming, self-biting, threats, tracking, and exploration time, and increases in self-clasping and frequency and duration of inappropriate behavior, compared to saline. Amphetamine increased exploration, stereotypy, vocalization, spasms, threats, tracking, and inappropriate time, when compared to saline. Amphetamine was also associated with decreases in grooming, self-clasping, and self-biting. It should also be noted that for some measures (e.g., stereotypy, spasm, self-clasp, tracking) the changes in frequency of occurrence were in the same direction following amphetamine and hallucinogen administration and in the opposite direction following chlorpromazine treatment. These latter results are in general agreement with the placement of these drugs on a continuum of central nervous system activation coupled with behavioral arousal proposed by Winters and Wallach (1970). These investigators argued that both amphetamine and hallucinogens induce cortical excitation accompanied by increasing amounts of bizarre and inappropriate behaviors as treatments were compared along a continuum of CNS excitatory agents ranging from amphetamine to the hallucinogens.

Previous studies suggested that hallucinogens are associated with changes in perceptual-motor behavior, sometimes accompanied by "hallucinatory manifestations" (see Introduction). The behavioral categories of fear grimace, threat, and tracking were employed in the present study to detect such changes since these behaviors normally occur only in the presence of an appropriate stimulus. Although some of the hallucinogen doses were associated with increases in some of these measures, the increases were neither large enough nor consistent enough to warrant confirmation of the notion of "hallucinatory stimuli".

Mitchell (1972) has argued that since rhesus monkeys select and attend to objects in their environment by visually observing them, scores of the duration of looking behavior (exploration) should be taken into account in addition to gross behavioral measures such as threats, attacks, and grooms. In the present study, hallucinogens were associated with a decrease in exploration time (Fig. 1). This reduction in the time spent in exploration of the environment could possibly have been due to a shift in attention toward internally generated stimuli.

Nonetheless, the observers who scored the videotapes were usually able to distinguish whether *S* had received an hallucinogen or another drug by noting the qualitative changes in behavior. Hallucinogen sessions were discriminable from others by the presence of unusual and atypical behaviors such as convulsive body jerks, grooming with hand covering face, walking around cage with eyes closed, and ataxic locomotion. The behavioral scores reflect this qualitative change in that the largest increases in scores after hallucinogen treatment occurred in "unusual" behavior categories (e.g., inappropriate, both frequency and duration). These behaviors all occurred with a low frequency in non-drugged subjects. Thus, in the present experiment, the increase in the occurrence of some behaviors infrequently observed in non-drugged animals (spasm, inappropriate, stereotypy), accompanied by a decrease in exploration time, appeared to be the best overall indicator of hallucinogen administration.

Further work on the application of these objective scoring techniques to the study of the behavioral effects of hallucinogens is needed and this would serve to standardize and quantify descriptions of so-called "hallucinatory" behavior, heretofore only anecdotally reported. An objective behavioral profile that could be employed to distinguish the effects of hallucinogens from those of other classes of drugs would be useful in many psychopharmacological studies with primates.

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