Psychopharmacologia (Berl.) 32, 171—182 (1973)

Effects of Δ^9-THC, LSD-25 and Scopolamine on Continuous, Spontaneous Alternation in the Y-Maze

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Received November 9, 1972

Abstract. The effects of Δ^9-THC, LSD-25 and scopolamine on continuous, spontaneous alternation of the hooded rat in the Y-maze were determined. LSD and scopolamine decreased the number of arm entries (responsivity) while concomitantly reducing percent alternation. THC however, reduced responsivity and percent alternation more at the lower dose (1 mg/kg) when compared to control than at the higher dose (3 mg/kg). Only scopolamine induced a significant increase in stimulus perseveration. The results are discussed in relation to the advantages afforded by the continuous spontaneous alternation procedure.

Key words: Δ^9-THC — LSD-25 — Scopolamine — Continuous Spontaneous Alternation — Stimulus perseveration.

Conventionally, spontaneous alternation (SA) behavior in the T-maze has been described as the non-appetitive, sequential alternation of right and left turning responses on repeated trials at a level of significance greater than chance. However, in studies where manipulations of SA behavior are made, the use of the conventional two response, T-maze design may be undesirable because of certain conceptual and methodological limitations. On the conceptual level, data exist which strongly suggest that rats do not simply alternate turns (i.e. responses), but instead alternate stimuli (Dember and Fowler, 1958; Glanzer, 1953). However, in the conventional two-response, T-maze paradigm a rat must simultaneously alternate both responses and stimuli.

A number of methodological limitations exist with the conventional SA paradigm. First, the limited number of responses pose certain problems in reliable data analysis. Secondly, the *S* must be manually returned to the stem arm between the two runs thus, introducing a third problem—an interference factor. Under the influence of drugs there theoretically could be an interaction between "interference" and the pharmacologic agent. Other factors generally noted in SA studies include the imposition of specified arm confinement periods (ACP) as well as intertrial intervals (ITI) between consecutive "runs".

While it is possible to determine optimal ACP's and ITI's which ensure stable baseline performance, the behavioral effects of certain psychotropic drugs may be seriously altered by such interposed time periods and distractions. Consequently, drug effects on behavior could be masked or magnified.

The use of a continuous SA procedure similar to that utilized by Swonger and Rech (1972) circumvents certain of the above difficulties. *Ss* are allowed to alternate continously for 8 min without experimenter intervention in symmetrical, doorless Y-mazes. Correct alternation performance requires movement from one arm to another in such a manner that the response alternative chosen is the one arm not entered on the last two responses. Thus, in the continuous SA paradigm stimulus alternation may be assessed in the absence of response alternation and in the absence of the confounding influences of distractions, interference, ACP's and ITI's. Additionally, each *S* is free to regulate his response rate, thereby allowing either longer or shorter times to reconnoiter the two response alternatives before responding. Said differently, the *S* may withhold responding until such time as the information available in all the exteroceptive cues is sufficient to enable a decision.

Though SA may be viewed more empirically as a simple form of exploratory behavior (Dember and Earl, 1957; Montgomery, 1951), its conceptualization as an index of recent memory functioning not reliant on prior training, has been repeatedly noted (Dennis, 1939; Dember and Fowler, 1958; Dember and Millbrook, 1956; Morgan and Wood, 1943). Meyers and Domino (1964) suggested that scopolamine-induced disruption of SA behavior (as measured in the conventional manner) might be due to a loss of recent memory. Similarly, Parks (1965) utilized the SA paradigm to detect the amnesia potential of a series of anticholinergic agents. In view of the foregoing, the present investigation was conducted to ascertain the effects of certain memory altering psychotropic drugs on continuous SA behavior in the rat. The drugs investigated were Δ^9-tetrahydrocannabinol (Δ^9-THC), LSD-25 and scopolamine.

Method

Subjects. The *Ss* were 56 naive, male hooded rats (Blue Spruce), 100—110 days of age at the beginning of the study. Throughout the study *Ss* were housed singly, under standard conditions of temperature and lighting (off 7:00 p.m.—7:00 a.m.) and with *ad lib* access to food and water.

Apparatus. The doorless Y-maze units employed were constructed of 20-gauge galvanized sheet metal painted a flat rust red. Each of the three arms were set at angles of 120° and were 50.8 cm long, 17.7 cm wide and 20.5 cm deep. The mazes were set on 40-gauge brown, seamless paper placed on the floor. The paper was changed after each 8 min test period. All testing occurred in a lighted room with one observer present. A 50 db white noise was used to mask extraneous noises.

Procedure. The procedure was essentially that of Swonger and Rech (1972). All *S*s were given once-weekly 8 min trials in the Y-maze. Pilot studies revealed the possibility of habituated responding or activity decay on consecutive daily placements in the Y-mazes. Weekly activity levels, as reflected by arm entries, remained acceptably stable. Testing on a bi-weekly schedule did not reliably increase arm entry (responsivity) over that seen with one weekly testing.

Each arm of the maze was numbered —1, 2 or 3. The sequence of arm entries was recorded over the 8 min trials. Percent alternation for each rat was computed according to the formula: $P = 100 \times A/(N\text{-}2)$, where P denotes percent alternation, A is the number of correct alternations and N is the total number of arm entries (Swonger and Rech, 1972). N-2 refers to the total number of recorded responses minus the first two recorded arm entries. The original "placement" in arm 1 was arbitrarily counted as one *recorded* response. In order to receive a percent alternation score the *S* next had to move sequentially into two consecutive arms. Without further requirements only one of two possible scores (0 or 100% alternation) could be computed. By increasing the requirement to 2 additional responses (i.e. recorded responses) scores of 0, 33.3, 66.6 or 100% become possible. Thus, in order to be included in statistical computations of percent alternation, any given *S* had to receive at least 5 recorded responses, whereas for the computations on total responses, all *S*s were used. Averaging the individual percent alternation scores within a treatment cell weights the average toward inactivity (Swonger and Rech, 1972).

Design. The experiment required 10 weeks for completion. In order to control for possible changes in responsivity and alternation across weeks, basal (no treatment) SA measures were taken during weeks 1, 2 and 9 on all *S*s. At the end of the second week the *S*s were randomly divided into seven groups of 8 *S*s each. One group received saline across the next 6 weeks (i.e. weeks 3—9). The remaining 6 groups were cast into a latin square design for drug treatment in order to evaluate the effects of the agents employed. Week 10 served to evaluate the effects of the Tween vehicle. Two dose levels of each drug were employed; Δ^9-THC (1 and 3 mg/kg), LSD-25 (0.048 and 0.14 mg/kg) and scopolamine (0.1 and 1.0 mg/kg).

Drugs. (—)-*trans* Δ^9-tetrahydrocannabinol suspended in sterile 1% Tween 80-water was prepared fresh daily at a concentration of 2 mg/ml; details reported elsewhere (Drew *et al.*, 1972). Sterile 1% Tween 80-water served as the vehicular control. Lysergic acid diethylamide bitartrate and scopolamine hydrobromide as the active bases were dissolved in sterile 0.9% saline which also served as a control for the latter drugs. All drugs were administered intraperitoneally 30 min prior to testing. Injection volumes were less than 1 ml.

Results

Under basal (no-treatment), Tween or saline treatment conditions *S*s behaved similarly. Thus, following a transient orientation response (rearing, sniffing and sometimes defecation) *S*s would quickly begin maze exploration. With few exceptions *S*s would traverse the entire length of the chosen arm, rear several times, sniff, turn around and then exit that arm to another and repeat the sequence. During later minutes of the 8 min test period, arm traversals were slower, but unexpectedly the *S*s would traverse almost the entire arm length. Generally, reductions in rearing and sniffing and increased grooming were noted on later arm entries. Basal responsivity (as measured by

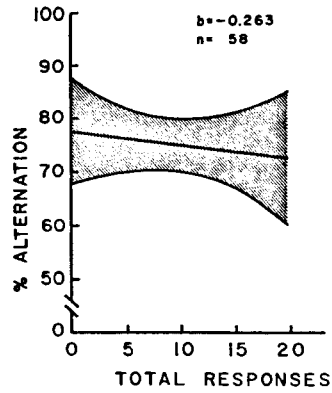

Fig. 1. Relationship of percent alternation to responsivity. The data used in computing the regression line and the 95% confidence band were obtained from the saline treatment group data collapsed across 6 weeks. The slightly negative slope ($b = -0.263$) was contained within the 95% confidence interval for b which ranged from -1.312 to 0.786

arm entries) was reliably high during the 8 min trials and accordingly percent alternation values (on animals with at least 5 or more recorded responses) generally ranged from 70 to 80%, rates significantly greater than chance ($p < 0.001$). The relationship between responsivity (total recorded responses) and percent alternation, was examined by a regression analysis performed on the data obtained from the saline treatment group collapsed across weeks. As shown in Fig. 1 the analysis revealed a slightly negative slope ($b = -0.263$) contained within the 95% confidence interval ($b = -1.312$ to 0.786). The figure also shows the 95% confidence band from 0 to 20 responses since most *S*s fell within this range. No essential differences existed between these saline values and those observed in the basal state during weeks 1, 2 and 9. Moreover, an analysis of the behavior of the saline treatment group across weeks indicated no significant decrease in the total number of responses or alternation compared to initial and basal values. The relatively constant alternation mean of 75% suggests that maze habituation may not occur upon once-weekly testing and therefore is not a factor to be contended with in analyses of drug treatments.

The effects of drug treatment on responsivity and alternation are summarized in Table 1. An unweighted means analysis of the latin square design (Kirk, 1969) revealed, as expected, no significant order effect ($0.10 < p < 0.25$) across weeks. For the six drug dosage conditions in the latin square design for total responses a significant main effect

Table 1. Effect of drug treatment on responsivity and percent alternation in continuous spontaneous alternation in the Y maze

Treatment	Responsivity			Alternation		
	mean individual responses ± S.D.	orthogonal comparison (t-values) with vehicle	regression coeff. (r)	mean individual % alternation ± S.D.	orthogonal comparison (t-values) with vehicle	regression coeff. (r)
Saline	10.35 ± 5.77 (66)			75.40 ± 17.03 (58)		
Scopolamine						
0.1 mg/kg	8.19 ± 5.67 (48)	1.973 [112]		66.84 ± 19.72 (32)	2.131* [96]	
			−0.068			−0.186
1.0 mg/kg	6.96 ± 5.87 (48)	3.049** [112]	(48)	58.29 ± 19.23 (24)	3.933** [88]	(19)
LSD						
0.048 mg/kg	6.63 ± 4.93 (48)	3.584** [112]		68.82 ± 24.12 (28)	1.440 [90]	
			−0.171**			−0.341*
0.14 mg/kg	5.21 ± 3.22 (48)	5.525** [112]	(48)	59.96 ± 26.19 (24)	3.119** [88]	(18)
Tween 80-water	14.07 ± 5.12 (44)			71.95 ± 15.78 (44)		
Δ^9-THC						
1.0 mg/kg	6.83 ± 5.13 (48)	6.689** [90]		64.92 ± 9.59 (26)	2.029* [68]	
			+0.055			+0.195
3.0 mg/kg	9.29 ± 14.70 (48)	2.023* [90]	(48)	70.32 ± 20.07 (28)	0.378 [70]	(22)

* $p < 0.05$; ** $p < 0.01$.

Numbers in parentheses ( ) are number of *Ss* used to compute that value. For responses all *Ss* were employed; for percent alternation only those *Ss* exhibiting 5 or more responses were included. Under orthogonal comparisons numbers are t-values while numbers in brakets [ ] denote degrees of freedom. For regression analyses (dose vs responses) all *Ss* were included. For regression of dose vs alternation only those *Ss* exhibiting 5 or more responses at *both* the high and low dose levels were analyzed.

for drugs was found ($F = 2.48$, $df = 5.252$, $p < 0.05$). However, there were no differences in responsivity between the six groups of rats ($F = 2.04$, N.S.). No effects on percent alternation were found for drugs, weeks or groups.

Taking the basal values and the vehicular effects into account, a one-way analysis of variance for total responses was applied to the six drug, three basal (no-treatment) controls, Tween and saline conditions. Drug treatment significantly changed total responses ($F = 20.25$, $df = 10.428$, $p < 0.01$) as well as percent alternations ($F = 2.25$, $df = 10.361$, $p < 0.05$).

Orthogonal comparisons of the three drugs at each dose level with their respective vehicles revealed that all drug treatments significantly depressed responsivity in comparison with control with the exception of the low dose level of scopolamine. A large variability in responsivity was noted at the highest dose level of THC employed, which for data validity becomes a factor generally limiting the employment of higher dose levels of this agent.

Both dose levels of scopolamine reliably reduced percent alternation. Only the high dose of LSD did so. With both scopolamine and LSD the alternation percentage was depressed in a dose-related manner. Under the influence of THC a different picture obtained. Only the low dose level reliably decreased correct alternation performance. With the higher dose less reduction in responsivity and alternation were observed than with the lower dose. However, the increased variability in responsivity at the highest dose level clouds a more precise evaluation of the effect of THC on alternation.

Reductions in alternation coincident with reduced levels of responsivity would suggest that impaired alternation performance may be due to locomotor depression. To aid in examining this possibility individual regression analyses (where dose was regressed separately against total responses and percent alternations) were computed for each drug. The regression coefficients obtained are also found in Table 1. As above, the data from all *S*s were examined for responses, but only those *S*s exhibiting 5 or more responses at *both* high and low dose levels of a drug were employed in computing the correlation coefficients on percent alternation. Scopolamine reduced responses (N.S.) and percent alternations (N.S.) with increasing dosages. For LSD these correlations were significant. With THC the correlations for response and alternation with dose were positive, but were non-significant despite the fact that mean responsivity was increased (from 6.8 to 9.3). Concomitantly, the increase in percent alternation was small (64.9 to 70.3%). Thus, impaired locomotor performance may contribute to impaired SA performance under LSD.

Currently, a controversy exists as to whether or not scopolamine induces response perseveration in the SA behavior of rats in T-mazes (see: Meyers and Domino, 1964; Leaton and Utell, 1970; Douglas and Isaacson, 1966). The conceptualization of perseverative responding within the continuous SA paradigm in the Y-maze is quite different than that in the T-maze. In the Y-maze correct alternation requires that the *S* alternate sequentially between three different stimuli (arms) while persevering turns. For example, an *S* makes a right turn to enter an arm and on exiting that arm again turns to the right, this exact sequence being repeated in each arm until the maze is circumnavigated, in this case in a counterclockwise direction. Thus, an *S* persevered in turns (R-R-R) in order to alternate stimuli. In order to be equated with the concept of perseverative 'responding' as applied to T-maze paradigms, perseverative behavior in the Y-maze paradigm would actually mean that an *S* would perseverate stimuli (arms) instead of responses (turns). Thus, in order to assess the potential of each agent to induce stimulus perseveration a response-by-response examination of each individual record was performed. For inclusion in the compilation of stimulus perseverations, an *S* had to exhibit 4 or more recorded responses and thus was considered "at risk" to commit a perseverative error (PE). One PE was recorded if, in a sequence of responses, 3 consecutive errors were accumulated. Any further increase in the chain of errors increased the PE count by one for each error. For example, recorded responses of 1,2,3,2,1,2,1,2,1,2,1,3 would yield a PE score of 4. The capacity of drug treatments to induce

Table 2. Effect of drug treatment on perseverative errors (PE)

Treatment	Number				% of *S*s committing PE of population at risk
	*S*s in sample	*S*s at risk to make PE	*S*s making PE	PE	
Saline	72	58	6	6	10.3
LSD					
0.048 mg/kg	48	28	2	3	7.1
0.14 mg/kg	48	25	5	5	20.0
Scopolamine					
0.1 mg/kg	48	33	6	6	18.2
1.0 mg/kg	48	27	12	22	44.4*
Tween	44**	44	9	18	20.5
THC					
1 mg/kg	48	26	4	9	15.4
3 mg/kg	48	28	5	12	17.9

* $p < 0.001$.

** Instead of 48 *S*s, only 44 were tested under Tween because of sickness.

stimulus perseveration is shown in Table 2. From the original samples of *Ss* under each drug treatment, certain subsamples of *Ss* were observed to be at risk to commit a PE. No real difference existed in the size of the "at-risk" samples across drug treatments. The largest number of *Ss* committing PE's occurred under the highest dose level of scopolamine (i.e. 12 of 48 or 25% of *Ss*). However, all *Ss* (48) were not at risk to commit a PE. Computed from the sample at risk to commit these errors this value increases to 44.4% which is reliably different ($p < 0.001$) from saline percentages (uncorrelated percentage test, Garrett and Woodworth, 1962). Compared to controls no other agent reliably increased PE's.

Discussion

The present study clearly demonstrates the advantages of the continuous, Y-maze procedure over that of the conventional, two-response T-maze paradigm for the study of SA behavior. The advantage of being able to simultaneously monitor "responsivity" as well as percent alternation in the continuous SA paradigm permits the direct examination of the correlation between responsivity and percent alternation. This relationship is important especially where the influence of pharmacologic agents is involved. Moreover, since responsivity as well as percent alternation are recorded over 8 min periods the data obtained are inherently more reliable than in the two-response paradigm where SA behavior is literally an "all or nothing" response. With the conventional T-maze paradigm percent alternation must be derived from group means whereas with continuous SA, individual percent alternation values may be obtained. The availability of individual SA means is essential for assessing stimulus perseveration since one may determine not only the percent of the total sample showing PE's but, precisely define that sample of *Ss* at risk to commit a PE. In the conventional T-maze design the entire population of *Ss* must be considered at risk to make PE's, an unjustifiable assumption. The continuous procedure would also lend itself well to studying the degree of severity of stimulus perseveration.

In the present study the effects of scopolamine, LSD and Δ^9-THC on continuous SA behavior in the rat were determined. The basal and saline control SA values, as well as the effects of scopolamine and LSD on SA remarkably corroborate the findings of Swonger and Rech (1972). The nearly identical data obtained in these two studies indicate that the continuous SA paradigm is highly reliably, since precise agreement between laboratories is obtainable.

It is well known that anticholinergics will disrupt two-trial SA behavior in the T-maze (Meyers and Domino, 1964; Parkes, 1965;

Douglas and Isaacson, 1966; Leaton and Utell, 1970). The results of the present study, as well as those of Swonger and Rech (1972), indicate that the sensitivity of the continuous SA procedure to anticholinergics is equal to or probably greater than that observed in the T-maze. A comparison of the present data with that of Leaton and Utell (1970) for example, a two-response, T-maze design including a 10 sec ACP, reveals some subtle and marked differences obtainable with these two paradigms. Leaton and Utell report that under saline conditions, 90 day old Sprague-Dawley rats exhibit an SA mean of approximately 90%. With the continuous SA procedure we observed a saline control mean of 75.4 $\pm$ 17 (S.D.) percent with a mean of 10.3 $\pm$ 5.7 (S.D.) responses across weeks (Table 1). Even with the advantageously higher control SA percentage Leaton and Utell report that scopolamine HBr at dose levels of 0.1 and 0.7 mg/kg (active base?) did not reduce percent SA significantly from control, but at 1.2 mg/kg, scopolamine significantly reduced alternation (to 70%). We found that 0.1 mg/kg scopolamine HBr (as the active base) significantly reduced percent SA from 75 to 66.8% without a significant reduction in responsivity (Table 1). With 0.13 mg/kg Swonger and Rech observed reductions from 75 to 55.7%. Under 1.0 mg/kg in the present study, percent alternation was reduced to 58.2%, in close agreement with Swonger and Rech. Reductions to 58% were not obtained in the T-maze design until the dosage reached 1.5 mg/kg (Leaton and Utell, 1970). These findings suggest a greater sensitivity to low doses of anticholinergics with the continuous SA procedure than is obtainable in the T-maze paradigm.

However, other studies utilizing the conventional two-response SA paradigm present divergent results. Parkes (1965) found that scopolamine (0.1 mg/kg) significantly interfered with SA on 50% of the trials. From the control or saline data presented in that study a group mean alternation of 82.7% may be calculated. Under 0.25 mg/kg (1 h post-injection) this was reduced to 55.5%. Parkes did not specify an ITI nor did he employ an ACP. Meyers and Domino (1964) found that 0.13 mg/kg scopolamine HBr (as the active base) reduced chance levels of alternation to 49% whereas with 1.05 mg/kg, no further reduction occurred. Meyers and Domino utilized a two response procedure with an attending ITI of 30 sec. These findings suggest that the presence or absence of ACP's (compare Leaton and Utell, 1970, with Parkes, 1965) as well a the presence of near absence of ITI's (compare Meyers and Domino, 1964, with Parkes, 1965, or Leaton and Utell, 1970), can seriously affect the influence of both small and large dose levels of anticholinergics. The continuous SA paradigm clearly avoids these confounding variables.

Meyers and Domino (1964) suggested that scopolamine-induced disruption of SA behavior might be explainable on the basis of an anti-

cholinergically mediated disturbance in medial temporal lobe structures, particularly the hippocampus. A parallel between the effects of scopolamine and hippocampectomy was suggested by Douglas and Isaacson (1966). Several T-maze studies suggest that both hippocampectomy and anticholinergic drugs can induce response perseveration (Douglas, 1967; Douglas and Isaacson, 1964; Roberts *et al.*, 1962). However, Leaton and Utell (1970) report that scopolamine reduced alternation, but did not produce response perseveration. In the present investigation scopolamine, at the high dose, induced stimulus perseveration in 25% of the total sample, or in 44.4% of those *S*s actually at risk to commit these errors. Thus, across the 10 fold increase in dose, percent alternation was reduced 13% (66.8% to 58.2%), while the number of *S*s exhibiting PE's in the population at risk more than doubled (from 18.2% to 44.4%; see Table 2), indicating that scopolamine *can* induce stimulus perseveration.

Swonger and Rech (1972) found that LSD at doses of 25, 75 and 150 µg/kg reduced continuous SA in the Y-maze in a dose-dependent manner. The data obtained in the present study are in precise agreement with this report. LSD-25 depressed percent alternation to the same extent as that seen under scopolamine, but reduced responsivity further. Stimulus perseveration was not significantly affected. The data of the present study lend support to the hypothesis of Swonger and Rech (1972) that SA may be controlled by "closely integrated" cholinergic systems.

The effects of Δ^9-THC on SA are different from the effects of either scopolamine or LSD. Under the low dose level (1.0 mg/kg) THC significantly reduced responsivity and percent alternation compared to control values under 1% Tween 80-water. However, at the highest dose level (3 mg/kg) THC produced a significant reduction in responsivity without significantly affecting percent alternation. Thus, at the higher dose less depression in both responsivity and percent alternation were observed. Based on earlier studies of locomotor activity (Drew *et al.*, 1972), it would appear that the greater responsivity observed in the present study is not artifactual, but instead represents an established effect of THC at this dose and time interval. THC induced stimulus perseveration but only in 15—17% of the *S*s at risk and is thus non-significant. However, it is unclear whether this value is accurate in view of the PE's observed under vehicular conditions.

Spontaneous alternation has been viewed as a means of studying recent memory functioning in a situation that does not require prior training (Parkes, 1965). For whatever other factors may be involved, this type of memory appears to be dependent also on exteroceptive cues. Within the context of continous SA an *S* is able to reconnoiter the response alternatives until exteroceptive stimulus information is

sufficent to enable a decision. Even in the face of rich exteroceptive input, scopolamine, LSD and the low dose of THC disrupted SA behavior. However, SA behavior of *S*s under the influence of the high dose level of THC was little changed from control. In alternation paradigms thought to be reliant almost totally on interoceptive cues, as in the case of non-spatial single alternation in the runway, THC significantly disrupts alternation performance in a linear, dose-dependent manner (Miller *et al.*, 1973). Taken together these data would then suggest that low doses of THC may disrupt both exteroceptively and interoceptively cued behavior, whereas with high dose levels only interoceptively cued behavior is impaired. This hypothesis is strongly supported by recent evidence indicating that only lower dose levels of THC selectively impair human short term memory whereas little impairment is observed with higher dose levels (Klonoff *et al.*, 1973).

Acknowledgements. The authors are grateful to R. M. Taylor for technical assistance and to David Marx and Louis Stark for assistance in the statistical analyses. This research was supported by U.S.P.H.S. Grant No. RO1-MH-18392-02.

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