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Repeated Acquisition of Behavioral Chains: Effects of Methylphenidate and Imipramine[1]

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THOMPSON, D M. *Repeated acquisition of behavioral chains effects of methylphenidate and imipramine.* PHARMAC. BIOCHEM BEHAV 4(6) 671–677, 1976. – A method involving repeated acquisition of behavioral chains was used to assess the effects of methylphenidate and imipramine in individual animals Pigeons obtained food for completing a 4-response chain, which was changed from session to session. Learning was defined by the decrease in errors across trials within a session, overall accuracy was measured by total errors per session For comparison, the drug tests were also conducted under a performance condition, in which the 4-response chain was the same from session to session. In general, both drugs increased total errors per session as a function of dose under both the learning and performance conditions. The error-increasing effect was greater with imipramine than with methylphenidate and was detected at lower doses under the learning condition than under the performance condition Under the learning condition, the higher doses of both drugs decreased the rate of within-session error reduction. Although neither drug enhanced accuracy at any of the doses tested, the lower doses of methylphenidate slightly decreased total trial time under both the learning and performance conditions

Acquisition Performance Behavioral chains Methylphenidate Imipramine

A previous study from this laboratory [12] assessed the acute effects of varying doses of *d*-amphetamine on learning by using a new method in which each animal served as his own control. The method involved the repeated acquisition of behavioral chains. Pigeons worked for food in a chamber containing 3 response keys. All 3 keys were illuminated at the same time by 1 of 4 colors. For each session the pigeon's task was to learn a new 4-response chain by pecking the correct key in the presence of each color. Drug administration began after total errors per session and within-session error reduction (learning) had stabilized. The highest dose of *d*-amphetamine (4 mg/kg) was found to impair overall accuracy and to decrease the rate of learning; lower doses either produced progressively less impairment or had no effect.

The present research used this method of repeated acquisition to assess the acute effects of varying doses of 2 other stimulant/antidepressant drugs, methylphenidate and imipramine. To permit additional comparisons, the drugs were also tested under a performance condition, in which the 4-response chain was the same from session to session. The only previous study of the effects of methylphenidate on learning and performance in pigeons [13] involved chronic administration of fixed doses. Imipramine was studied because (1) previous research with pigeons under other learning and performance conditions (e.g., [1,11]) had indicated that imipramine-like compounds were capable of producing substantial error-increasing effects and (2) a direct comparison of the behavioral effects of imipramine and methylphenidate is currently of clinical interest (e.g., [9]).

METHOD

Animals

Three adult male White Carneaux pigeons (Nos. 2276, 7 and 8) were used. All had been used previously in drug experiments involving the repeated acquisition and performance of response sequences [12, 13, 14, 15]. The pigeons were maintained within 10 g of 80% of their free-feeding weights throughout the research by food presented during the sessions and by post-session supplemental feeding. The 80% values ranged between 470 and 510 g. Water and grit were always available in the home cages.

Apparatus

A standard 3-key pigeon chamber (Lehigh Valley Electronics, Model 1519B) and connecting automatic control equipment were used. Each translucent response key required a static force of 18 g (0.177 newton) to close the microswitch. Each key could be transilluminated by three Sylvania 24ESB indicator lamps, one with a red plastic end cap, one with a green cap and the third with no cap. All three keys were illuminated at the same time by the same

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color, either white, red, green or yellow. The yellow (actually yellow-orange) was produced by the red and green lights being on simultaneously. The scheduling of events was accomplished by means of timers, steppers and associated relay circuitry, the recording was by counters, a running-time meter, and an 11-pen event recorder. White noise was continuously present in the chamber to mask extraneous sounds.

Procedure

Throughout the following procedures, the primary reinforcer was food (5 sec access to mixed grain). Presentation of the reinforcer was accompanied by the offset of the keylights and the onset of the light in the food magazine. Each session terminated after 40 food reinforcements. A blackout (all lights off) of variable duration preceded and followed each session. With few exceptions there were 7 daily sessions a week.

Baseline conditions. All 3 response keys were illuminated at the same time by 1 of 4 colors, either yellow, green, red or white. The pigeon's task was to peck the correct key in the presence of each color, e.g., keys yellow – Left correct, keys green – Right correct; keys red – Center correct, keys white – Right correct, reinforcement. The same chain (in this case, Left-Right-Center-Right or LRCR) was repeated throughout a given session and each completion of the chain was considered a trial Food reinforcement was on a fixed-ratio (FR 5) schedule the completion of every fifth trial was followed by 5 sec access to grain The completion of all other trials was followed by a 0.5 sec presentation of the food magazine. The number of correct responses per session was fixed 4-response chain on an FR 5 schedule for 40 food reinforcements = 800 correct responses. When the pigeon pecked an incorrect key (a key not included in the 4-response chain), the error was followed by a 5 sec timeout. During the timeout, the keylights were off and a response had no effect An error did not reset the chain, i.e., the keylights after the timeout were the same color as before the timeout.

When the repeated acquisition baseline (learning) was in effect, the 4-response chain was changed from session to session. The chains were carefully selected to be equivalent in several ways and there were restrictions on their ordering across sessions (see [12]). An example of a typical set of 6 chains is as follows LRCR, CLRL, LRLC, RCRL, CLCR, RCLC; the order of the associated colors was always the same. yellow, green, red, white (food on the FR 5 schedule).

Each pigeon was also exposed to a performance baseline, in which the 4-response chain was the same from session to session. Different chains were arbitrarily selected for the three pigeons CLRC for No. 2276; CRLR for No. 7, RCRL for No. 8.

Drug testing Before the drug testing began, the baseline (either learning or performance) was stabilized. The baseline was considered stable when total errors per session and within-session error rates no longer showed systematic change from session to session. Such stabilization required 30–40 sessions under the learning condition and 15–20 sessions under the performance condition. After stabilization under a given condition, the next 12 weeks were used to obtain dose-effect data for methylphenidate hydrochloride and imipramine hydrochloride. Four doses of each drug were tested (2.5, 5, 10 and 20 mg/kg) and 2 determinations for each dose were taken with each pigeon. The drug testing followed the design MIIM, where M and I represent the blocks of 4 doses of methylphenidate and imipramine, within each block, the doses were tested in a random order. The drugs were dissolved in saline and injected into the pectoral muscles 30 min presession. Drug sessions were separated by 5 days, during which time there were baseline sessions and a control session (saline alone injected intramuscularly, 30 min presession). The volume of each injection was 0.1 ml/100 g body weight. The drugs were tested first under the learning condition and then under the performance condition with Nos. 7 and 8; the conditions were reversed with No 2276

RESULTS

Figure 1 shows the effects of varying doses of imipramine and methylphenidate (both determinations) on total errors per session under the learning and performance conditions Note the different scales on the ordinates for the 2 conditions. The drug data for individual animals were analyzed by comparing a given drug session with the saline sessions and all of the baseline sessions during drug testing except the one after the drug session. The brackets indicate the ranges of variability for the baseline (B) and saline (S) sessions. A drug was considered to have an effect on overall accuracy to the extent that the dose data fell outside of both ranges. The first and second determinations of the dose-effect curves yielded similar results (1) in general, both drugs increased total errors per session as a function of dose under both the learning and performance conditions, (2) the error-increasing effect of a given dose was greater with imipramine than with methylphenidate under both conditions, and (3) the error-increasing effect was detected at lower doses of both drugs under the learning condition than under the performance condition. Note the marginal nature of the methylphenidate increases in 2 birds under the performance condition

Figure 2 illustrates the within-session effects on accuracy obtained with imipramine and methylphenidate (10 and 20 mg/kg, first determinations) under the learning condition The errors are plotted cumulatively so that the rate of errors during a given part of a session can be estimated easily from the slope of the curve. The curves for the drug sessions should be compared to the saline (min) and saline (max) sessions Although there was a decrease in errors across trials (i.e., learning) during each session, error reduction generally occurred at slower rates in the drug sessions than in the saline sessions. There was less within-session error reduction at 20 mg/kg than at 10 mg/kg of each drug. The second determinations for these doses yielded similar results.

The change in error rate (negative acceleration) during each session shown in Fig. 2 was quantified by applying the Index of Curvature [5] to the cumulative data In computing the Index, each session of 200 trials was divided into 10 equal intervals of 20 trials each. If all the errors in a session occurred during the first 20 trials, the Index would take on its maximum value of −0.900. If the error rate were constant during the session, the Index would equal 0. The Index of Curvature values are shown in Table 1 (first column). In general, the degree of negative acceleration of error rate was less (smaller Index values) in the drug sessions than in both saline sessions. The only exception (No. 8, imipramine, 10 mg/kg) was related to the fact that

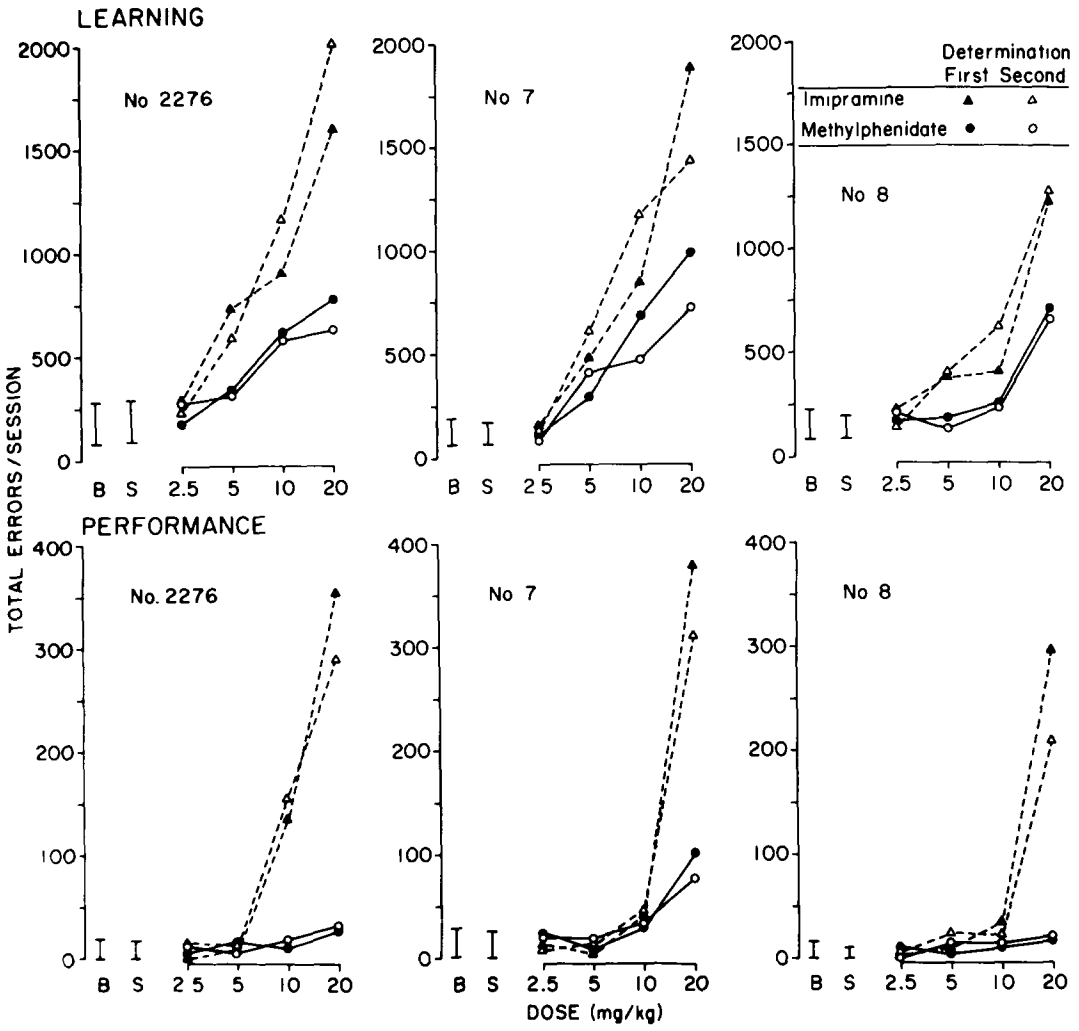

FIG. 1. Effects of imipramine and methylphenidate on total errors per session under the learning and performance conditions Under the learning condition, the 4-response chain was changed from session to session, whereas under the performance condition, it was the same from session to session Four doses of each drug were tested under each condition and there were 2 determinations for each dose with each of the 3 pigeons The brackets indicate the ranges of variability for the baseline (B) and saline (S) sessions.

the initial values (the number of errors in the first block of five trials shown in Fig. 2) were not the same under the saline and drug conditions. The initial values were equated as follows. For a given drug or saline (max) session shown in Fig. 2, a constant was subtracted from all of the data points so that these sessions had the same initial value as the saline (min) session. The index then was computed again, the values for the adjusted Index are shown in Table 1 (second column) On the basis of the adjusted Index, the degree of negative acceleration of error rate was less in the drug sessions than in both saline sessions for all 3 pigeons. Moreover, the adjusted Index revealed 2 other consistencies (1) there was always less negative acceleration in the saline session with the maximum total errors than in the saline session with the minimum total errors, and (2) at the same dose, there was always less negative acceleration in the imipramine session than in the methylphenidate session. Such consistencies point to a more general relationship, namely, the greater the total errors per session, the slower the rate of within-session error reduction

The Index of Curvature was not computed for sessions under the performance condition because only a few errors were made during the saline sessions (see Fig. 1, bottom), and the Index would be misleading in such cases [5]. Inspection of the event recordings indicated that the error rate under the performance condition was relatively constant across trials, but was higher in the drug sessions than in the saline sessions.

Although errors were the data of major interest, there were other behavioral measures affected by the drugs One of these was the total trial time per session (i.e., the total number of minutes that the keylights were on), which indicates the amount of pausing that occurred. Figure 3 shows the drug effects on total trial time per session under the learning and performance conditions. The first and second determinations yielded similar results· (1) Imipramine generally increased the total trial time per session as a function of dose under both the learning and performance conditions. The only exception was one

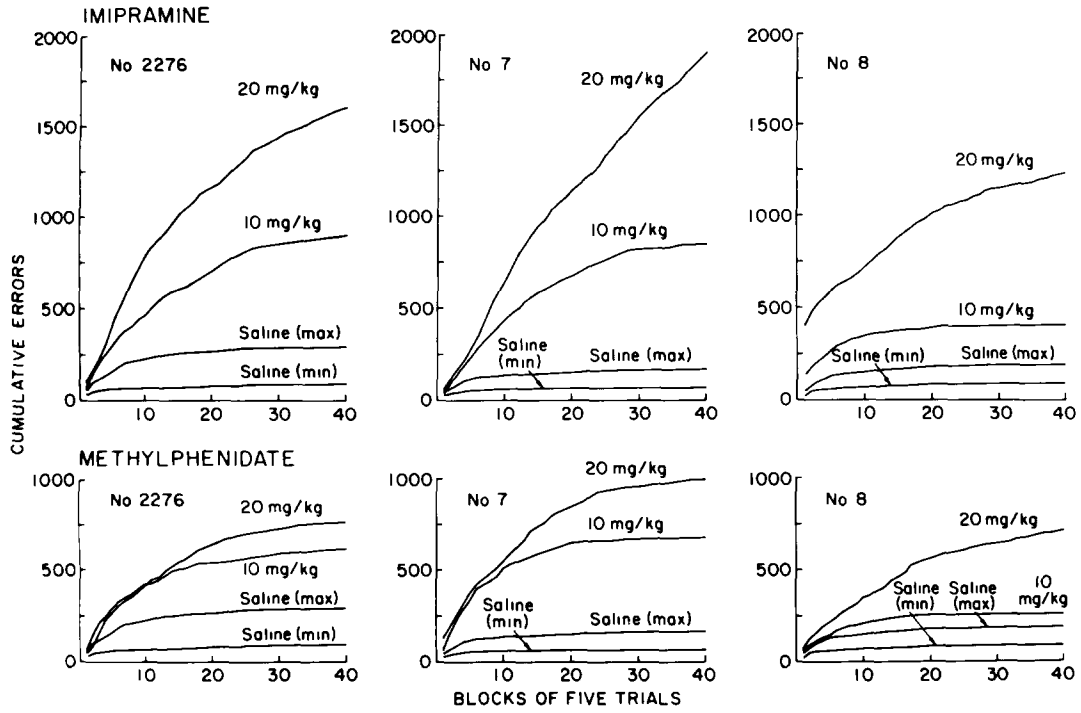

FIG. 2. Effects of the higher doses of imipramine and methylphenidate (first determinations) on within-session error reduction under the learning condition The saline (min) and saline (max) sessions were the sessions with the minimum and maximum total errors of all the saline sessions (16 for each pigeon) conducted during both determinations of the dose-effect curves.

instance in which there was a slight decrease in pausing (No 8, performance, 2 5 mg/kg, second determination). (2) With Nos. 2276 and 7, the pause-increasing effect was detected at lower doses of imipramine under the learning condition than under the performance condition. (3) Under both conditions, methylphenidate produced a slight decrease in total trial time per session at the lower doses, at the higher doses, methylphenidate either had no effect on pausing or produced an increase that was smaller than that produced by imipramine

A comparison of Fig. 3 with Fig 1 indicates that under both the learning and performance conditions, the doses of

TABLE 1

DEGREE OF NEGATIVE ACCELERATION OF ERROR RATE UNDER THE LEARNING CONDITION

Pigeon	Session	Index of Curvature	Adjusted Index
No 2276	Saline (minimum total errors)	−0 711	−0 711
	Saline (maximum total errors)	−0 671	−0 647
	Imipramine, 10 mg/kg	−0 415	−0 399
	Imipramine, 20 mg/kg	−0 318	−0 294
	Methylphenidate, 10 mg/kg	−0 550	−0 525
	Methylphenidate, 20 mg/kg	−0 444	−0 429
No 7	Saline (minimum total errors)	−0 746	−0 746
	Saline (maximum total errors)	−0 704	−0 679
	Imipramine, 10 mg/kg	−0 409	−0 403
	Imipramine, 20 mg/kg	−0 127	−0 116
	Methylphenidate, 10 mg/kg	−0 617	−0 602
	Methylphenidate, 20 mg/kg	−0 474	−0 428
No 8	Saline (minimum total errors)	−0 700	−0 700
	Saline (maximum total errors)	−0 706	−0 674
	Imipramine, 10 mg/kg	−0 703	−0 631
	Imipramine, 20 mg/kg	−0 471	−0 284
	Methylphenidate, 10 mg/kg	−0 685	−0 658
	Methylphenidate, 20 mg/kg	−0 363	−0 329

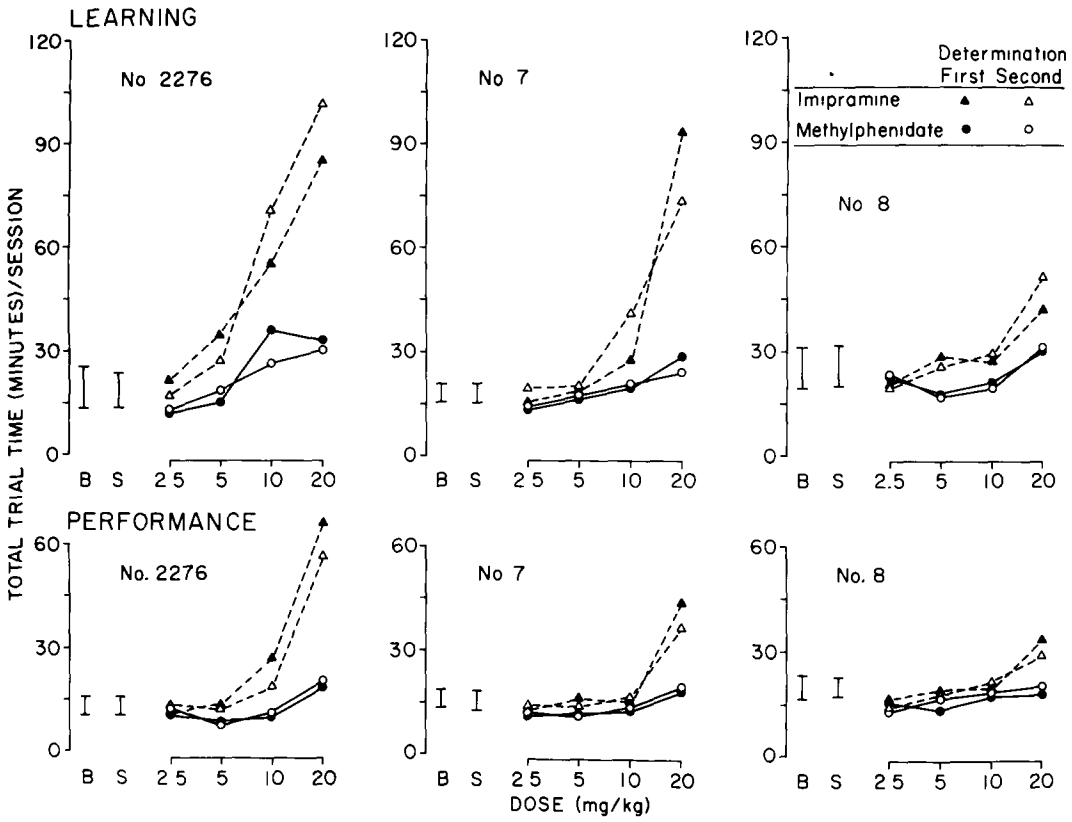

FIG 3. Effects of imipramine and methylphenidate on total trial time per session under the learning and performance conditions (See legend for Fig. 1)

methylphenidate that decreased pausing had no effect on accuracy. On the other hand, there were instances of accuracy being impaired (errors increased) by doses of both drugs that had no effect on pausing (e g , No. 7 at 5 mg/kg under the learning condition).

Another behavioral measure affected by the drugs was the timeout responses per session, i.e., the total number of responses made during the 5 sec timeout periods when the lights were off and a response had no effect. Figure 4 shows the drug effects on timeout responses per session under the learning condition. (Corresponding data obtained under the performance condition are not shown since virtually no timeout responses were made by any of the pigeons during either control or drug sessions.) The first and second

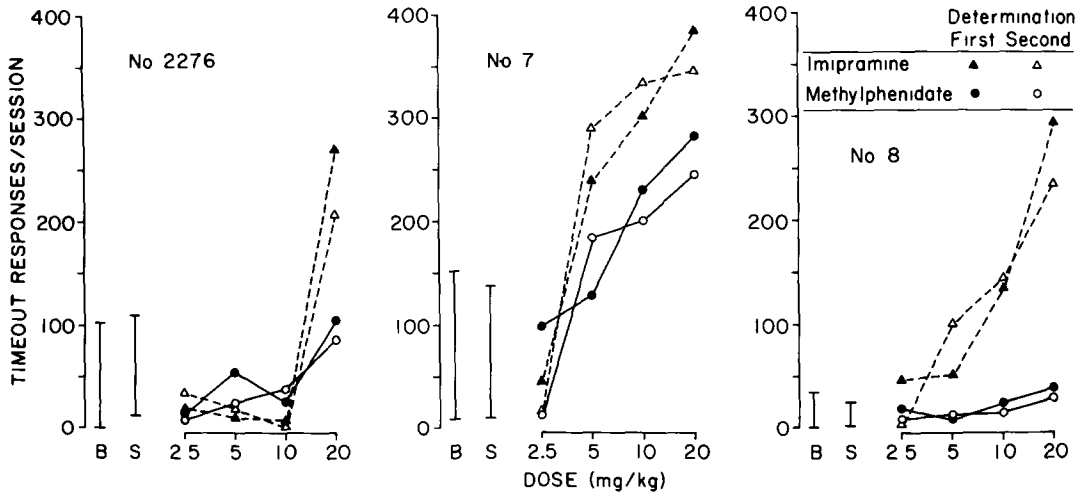

FIG 4. Effects of imipramine and methylphenidate on timeout responses per session under the learning condition. (See legend for Fig. 1)

determinations yielded similar results: imipramine increased timeout responses per session as a function of dose in all pigeons, whereas methylphenidate had this effect in only one pigeon (No. 7) A comparison of Fig. 4 with Fig 1 (top) indicates instances of errors being increased by doses of both drugs that had no effect on timeout responses (e.g., No. 2276 at 10 mg/kg).

DISCUSSION

The accuracy of pigeons working in a repeated acquisition procedure was affected by methylphenidate and imipramine in a manner similar to that found previously with *d*-amphetamine [12]. The highest doses of all 3 drugs impaired overall accuracy and decreased the rate of learning, lower doses either produced progressively less impairment or had no effect on accuracy. Although the drugs had the same type of effect on accuracy under the learning condition, one quantitative difference between methylphenidate and imipramine was apparent. The magnitude of the error-increasing effect was greater with imipramine than with the same doses of methylphenidate. The possibility exists, of course, that the dose-effect curves for the 2 drugs would have converged at doses higher than 20 mg/kg. The only apparent qualitative differences between the drugs under the learning condition (at the doses tested) involved their effects on total trial time and timeout responding. First, unlike imipramine, methylphenidate produced small but reliable decreases in total trial time at the lower doses. Second, unlike methylphenidate, imipramine generally increased timeout responding as a function of dose.

The disruptive effects of methylphenidate and imipramine on overall accuracy generally occurred at lower doses under the learning condition than under the performance condition. This finding is consistent with the widely held view that difficult tasks are more susceptible to drug effects than simple tasks [3, 8, 13, 14, 15, 18]. The fact that the control error levels under the learning condition were much greater than those under the performance condition indicates that learning was a more difficult task. The 2 conditions may also be considered as representing strong versus weak stimulus control (cf. [6]). Under the performance condition, the stimulus-response sequence remains constant from session to session and the animals are highly practiced. One would assume that this behavior is strongly controlled by the stimuli and would therefore be resistant to disruption by drugs. Under the learning condition, where the stimulus-response sequence is changed daily, stimulus control would be relatively weak and the behavior would therefore be more readily disrupted by drugs.

The results obtained with methylphenidate in the present research are in basic agreement with those obtained in a previous study of the behavioral effects of this drug in pigeons [13]. In that study, the repeated acquisition and performance of behavioral chains served as baselines for assessing the effects of chronic administration of methylphenidate. A fixed dose was administered each day (intramuscularly, 30 min presession) for a number of sessions or until behavioral tolerance developed, in which case the dose was doubled. Under the learning condition, the initial administration of each dose (5, 10 and 20 mg/kg) impaired overall accuracy; the magnitude of the effect increased with dose. Although total errors per session gradually returned to control levels during repeated administration of the lower doses, the error-increasing effect of the highest dose persisted. The chronic drug regimen produced less behavioral disruption under the performance condition than under the learning condition.

The substantial error-increasing effect obtained with imipramine in the present research complements the results obtained with imipramine-like compounds in pigeons under other learning and performance conditions For example, Bloomfield [1] found that desmethylimipramine (intramuscularly, 10 min presession) increased the incorrect responding of pigeons learning a "difficult left/right discrimination," as compared to a saline group Unlike the present research, however, Bloomfield tested only a single dose (5 mg/kg) and was therefore unable to draw any firm conclusions about the behavioral pharmacology of the compound used. In another situation, which involved the performance of pigeons on a discrimination between vertical and horizontal lines, Terrace [11] found that imipramine (1–17 mg/bird, intramuscularly, 30 min presession) increased errors as a function of dose, provided that the discrimination had previously been learned with errors The drug had no effect on performance accuracy if a fading procedure had been used to produce errorless discrimination learning. Results obtained with pigeons in a variety of other performance situations have indicated that imipramine can either increase or decrease response rate, depending on the dose, the schedule of reinforcement and the rate of ongoing behavior [2, 4, 7, 10, 16, 17, 19, 20]

Previous research in this laboratory [12, 13, 14, 15] has shown that repeated acquisition of behavioral chains provides a stable, sensitive and recoverable baseline for assessing the effects of drugs on learning in individual animals. This conclusion is further supported by the present research, which revealed certain similarities and differences, both qualitative and quantitative, between the behavioral effects of a stimulant (methylphenidate) and an antidepressant (imipramine) in pigeons.

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