Pharmacology Biochemistry & Behavior, Vol. 21, pp. 721–726, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Effects of Chlorprothixene, Haloperidol, and Trifluoperazine on the Delayed-Matching-to-Sample Performance of Pigeons[1]

ALAN POLING, MITCHELL PICKER AND JASPER THOMAS

Department of Psychology, Western Michigan University, Kalamazoo, MI 49008

Received 19 January 1984

POLING, A., M. PICKER AND J. THOMAS. *Effects of chlorprothixene, haloperidol, and trifluoperazine on the delayed-matching-to-sample performance of pigeons.* PHARMACOL BIOCHEM BEHAV **21**(5) 721–726, 1984.—The effects of chlorprothixene (4, 6, 8, and 10 mg/kg), haloperidol (0.13, 0.25, 0.38, and 0.5 mg/kg), and trifluoperazine (0.5, 1, 2, and 3 mg/kg) were examined in pigeons responding under a delayed-matching-to-sample procedure in which delays of 0.5-, 1-, 2-, 4-, and 8-sec duration were arranged during each experimental session. Both chlorprothixene and trifluoperazine typically reduced accuracy (percent correct responses); the magnitude of this effect was generally largest at the longest delay values. Chlorprothixene was associated with an increased rate of responding to the sample stimulus in two of three subjects, whereas trifluoperazine almost always decreased response rate. Haloperidol at high doses decreased response rate, but failed to consistently impair accuracy at any dose or delay value.

Delayed-matching-to-sample Chlorprothixene Haloperidol Trifluoperazine Neuroleptic drugs Pigeons

SINCE the mid-1950s, when chlorpromazine was introduced into psychiatric practice, many compounds have been tested for their ability to manage psychotic behavior. Drugs used for this purpose, known collectively as neuroleptics, antipsychotic agents, or major tranquilizers, currently number over 30 [1]. Most of these are phenothiazines, although certain thioxanthenes and butyrophenones also are effective neuroleptics [1].

Despite claims to the contrary, no one neuroleptic is clearly of superior clinical value. As Baldessarini notes, "Since the choice of a drug cannot be made on the basis of anticipated therapeutic effect, the selection of a particular medication for treatment often depends on side effects" ([1], p. 415). Clinical investigations have revealed a variety of deleterious side effects of neuroleptics, among the most serious of which are motor disturbances. Several reviews of the clinical efficacy and side effects of neuroleptics have appeared (e.g., [1, 4, 5]).

Attempts to delineate the actions and mechanisms of action of neuroleptics have not been confined to clinical investigations; many studies examining the behavioral and physiological effects of neuroleptics in nonhumans have appeared. However, relatively few studies have systematically compared the behavioral effects of various neuroleptics. It is not, for example, clear how many other neuroleptics resemble chlorpromazine in impairing the performance of nonhumans exposed to a delayed-matching-to-sample procedure [3, 5, 11]. This procedure is of some interest to behavioral pharmacologists in that it provides a sensitive assay of the effects of drugs on complex conditional discriminations and, perhaps more importantly, on what might be referred to as "short-term memory" (see [12]).

The purpose of the present study was to compare the effects of three neuroleptics, each representing a separate chemical class, on the performance of pigeons tested under a delayed-matching-to-sample (DMTS) procedure. The drugs examined were chlorprothixene, a thioxanthene, haloperidol, a butyrophenone, and trifluoperazine, a phenothiazine. A previous study [2] has shown that haloperidol at relatively high doses impaired monkeys' performance under a DMTS procedure, although the degree of impairment was not related to the delay interval. To our knowledge, no previous reports of the effects of chlorprothixene and trifluoperazine under a DMTS procedure have appeared.

METHOD

Subjects

Three experimentally-naive White Carneaux pigeons, maintained at 80% of their free-feeding weights, served as subjects. Each bird was individually housed with unlimited access to grit and water in a constantly illuminated room.

[1]The reported research was partially supported by Grant No. 1 RO1 NS20216-10 from the National Institutes of Health.

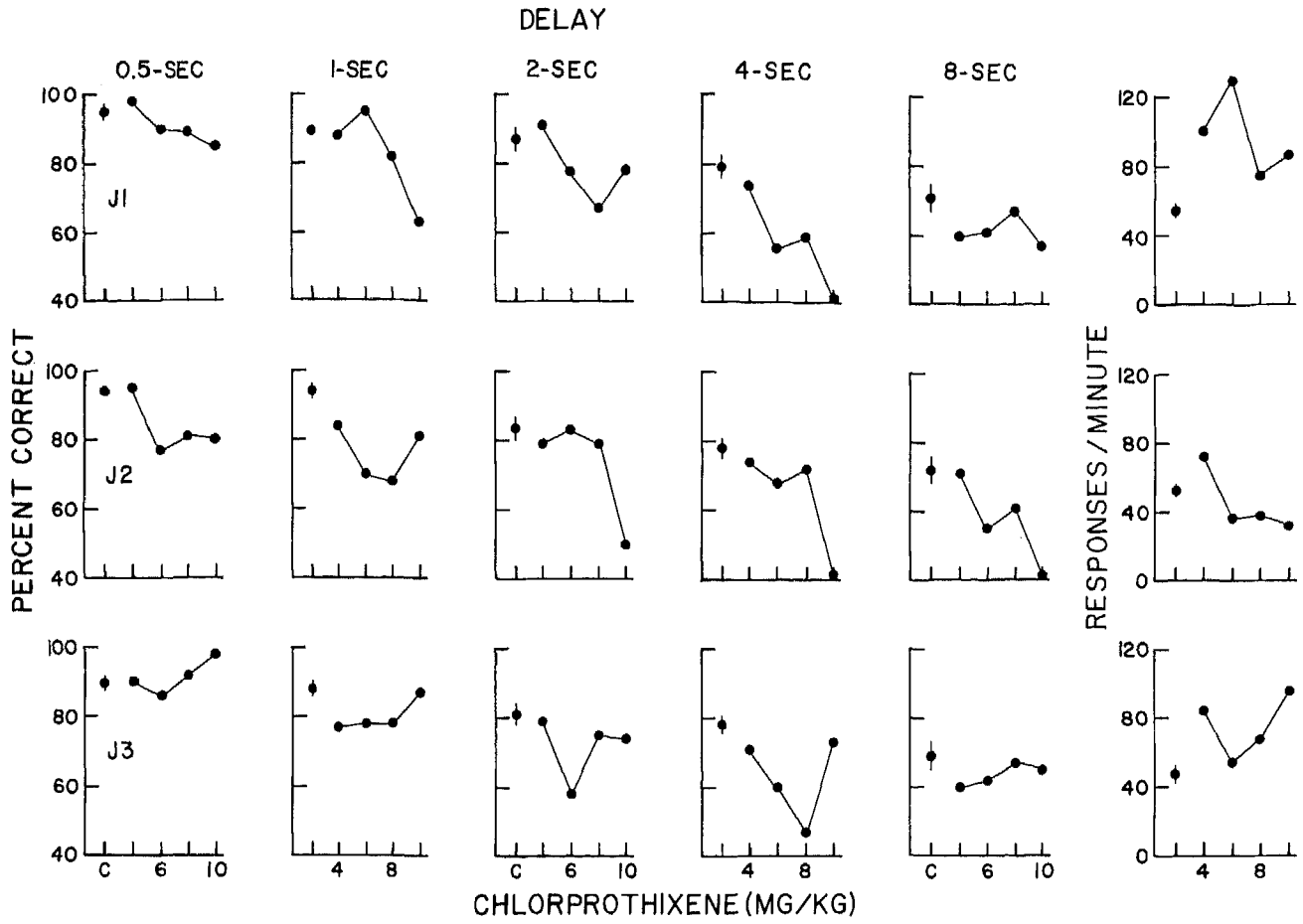

FIG. 1. Effects of chlorprothixene on percent correct responses and rate of responding to the sample stimulus (i.e., on the center key). Reading from left to right, the first five panels represent accuracy at each delay value (0.5, 1, 2, 4, and 8 sec). For these panels, control data (indicated by C) are expressed as the mean percent correct responses ([correct responses/correct responses + incorrect responses] ×100) for the 8 sessions that preceded drug administrations; vertical lines represent ±1 standard error of the mean. When vertical lines fail to appear, standard errors fall within the data point. Drug data are expressed as the percentage of correct responses for the two determinations at each dose combined. The panels at the far right show the mean rate of responding (responses/min) during the 8 sessions that preceded drug administrations (vertical lines represent ±1 standard error of the mean) and during the two administrations of each drug combined.

Apparatus

Three Lehigh Valley Electronics (BRS/LVE, Lehigh Valley, PA) operant conditioning chambers, measuring 32 cm long, 36 cm high, and 35 cm wide, were employed. In each chamber, three response keys 2.5 cm in diameter were located 23 cm from the bottom of the intelligence panel (front wall), approximately 5.5 cm apart. Each key could be illuminated in blue-green or red. A minimum of 0.2 g pressure was required for key operation. An aperture horizontally centered on the intelligence panel 7.5 cm above the floor allowed access to a hopper filled with mixed grain when the hopper was raised. When raised, the hopper was lighted by a 7-W white bulb. A 7-W white bulb centrally mounted 33 cm above the chamber floor provided ambient illumination and an exhaust fan supplied masking noise and ventilation.

Scheduling of experimental events and data collection were accomplished through the use of a Digital Equipment Corporation (Maynard, MA) PDP8/A minicomputer using interfacing and software (SUPERSKED™) provided by State Systems Inc. (Kalamazoo, MI).

Behavioral Procedure

Prior to the experiment proper, all subjects were trained to eat from the raised food hopper, then exposed to an autoshaping procedure described elsewhere [9]. Once keypecking was reliably established under the autoshaping procedure, birds were exposed to conditions in which discrete trials were programmed with a 10-sec intertrial interval (ITI). Each trial began with a 0.25-sec darkening of the chamber, following which the center key was illuminated in red or blue-green; center key illumination constituted presentation of the sample stimulus. A response to the center key turned off the sample stimulus and initiated a fixed duration delay interval of 0.5, 1, 2, 4, or 8 sec. During the delay period the houselight remained illuminated, responses had no programmed consequences, and the keys were dark. At the end of the delay period the two side keys were illuminated in 1 of 2 possible configurations of color and position (i.e., red on left key and blue-green on right key, or red on right key and blue-green on left key). Illumination of the side keys constituted presentation of the comparison stimuli. A response to

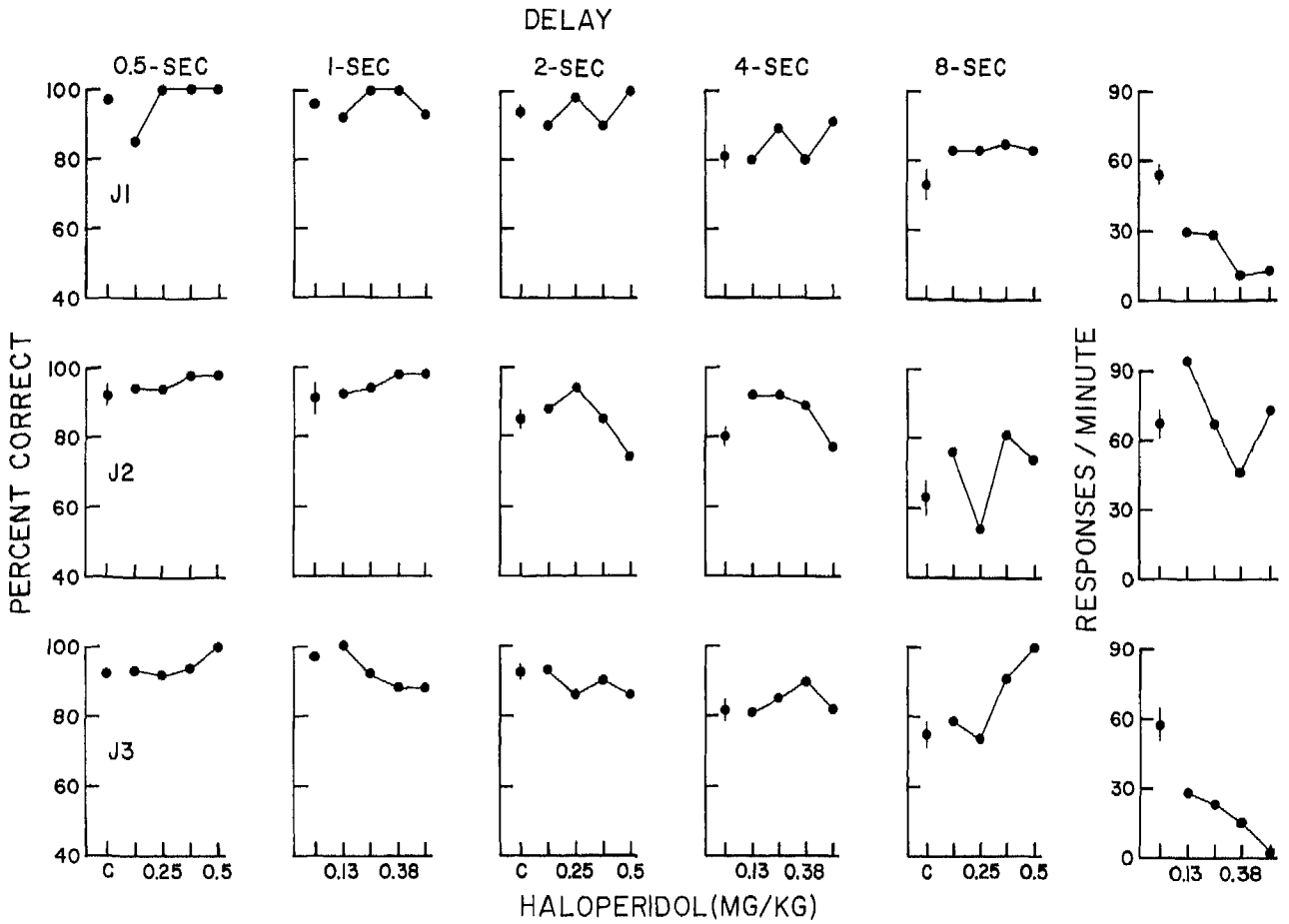

FIG. 2. Effects of haloperidol on percent correct responding and rate of responding to the sample stimulus. Details are as in Fig. 1.

the comparison stimulus which matched the sample stimulus in color darkened both side keys, provided 3-sec access to mixed grain, then initiated a 10-sec ITI. Trials terminated by a nonmatching response (error) also darkened the keys and initiated a 10-sec ITI. Such trials were repeated until the pigeon responded to the appropriate comparison stimulus. Repeating of trials in which errors were made was intended to prevent pigeons from developing position preferences (in the absence of a correction procedure, 50% of the available food deliveries could be earned simply by responding on one or the other side key).

When the percentage of correct responses ([matching responses/matching responses + nonmatching responses] × 100) for individual birds showed no visually evident trend across 10 consecutive 140-trial sessions, the response requirement for extinguishing the sample stimulus was lengthened to 5 (i.e., a fixed-ratio 5 schedule was arranged), and only every second correct response was followed by food delivery. Correct responses not followed by food were followed by a 1-sec flash of the hopper light. During each block of 10 trials, the red and blue-green stimuli appeared equally often as the sample (presentation was random except for this requirement), and each of the delay values appeared twice. Trials terminated if the response requirement for center-key pecks (i.e., those directed to the sample stimulus) was not completed within 35 sec of trial initiation, or if the subject failed to respond to one of the side keys within 35 sec of the onset of presentation of the comparison stimuli. Such aborted trials were repeated after a 10-sec ITI and were not recorded as incorrect responses. During the experiment proper, sessions terminated after 140 trials or 1 hour, whichever came first. Sessions were conducted 6 days per week, at about the same time each day.

Pharmacological Procedure

After 40 sessions of exposure to the DMTS procedure just described, the effects of chlorprothixene, haloperidol, and trifluoperazine were evaluated. Drugs were administered in a BCDBCD design where B represents baseline sessions (no injection), C vehicle control sessions, and D drug sessions. All drugs were injected as a commercially prepared solution diluted with isotonic saline solution to an injection volume of 1 ml/kg. Isotonic saline solution (1 ml/kg) was given as the control vehicle for all drugs.Chlorprothixene hydrochloride (Taractan™) was obtained from Roche Laboratories (Nutley, NJ), haloperidol (Haldol™) from McNeil Pharmaceuticals (Spring House, PA), and trifluoperazine hydrochloride (Stelazine™) from SmithKline Corporation (Philadelphia, PA).

Four doses of each drug and vehicle controls were injected intramuscularly 15 min prior to the experimental ses-

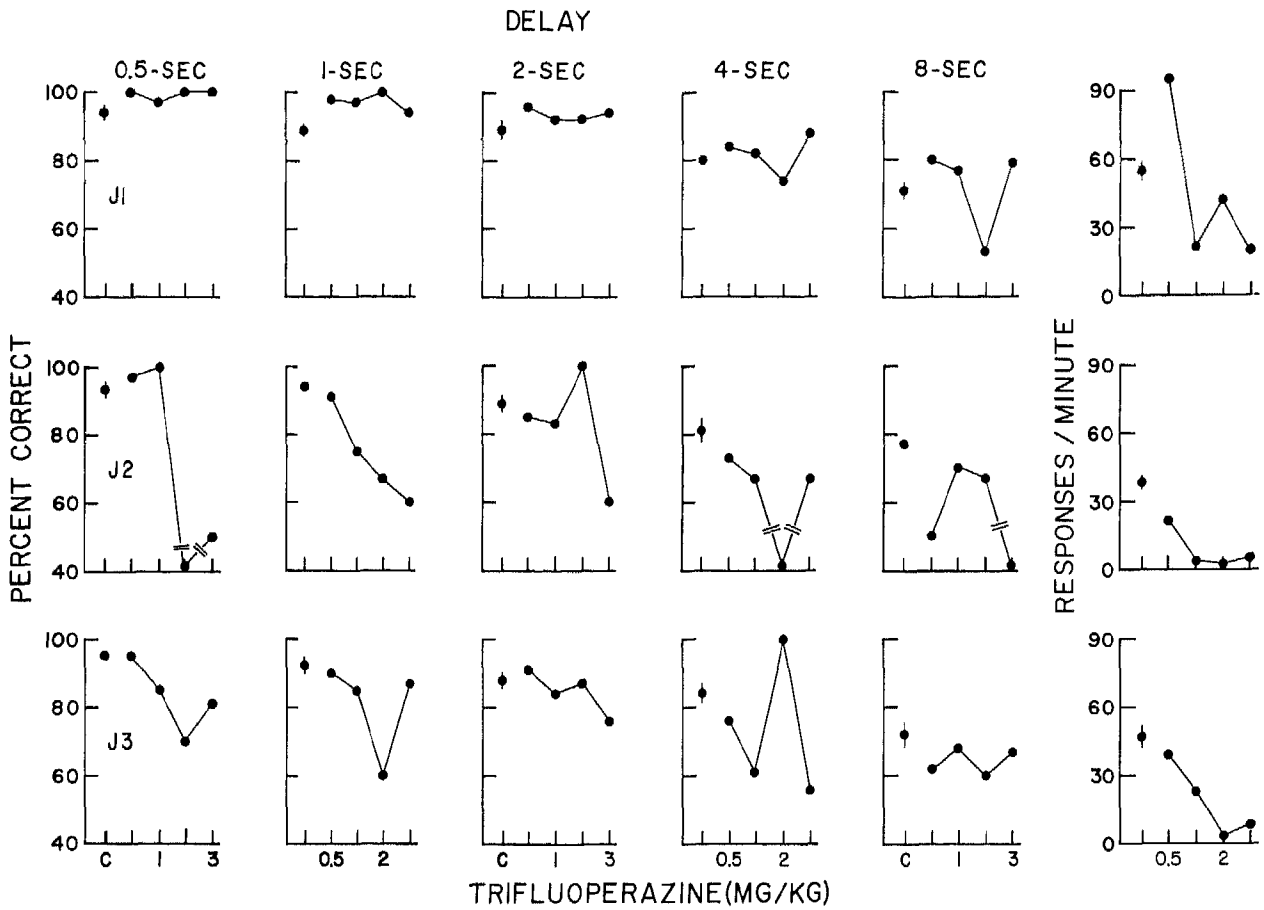

FIG. 3. Effects of trifluoperazine on percent correct responses and rate of responding to the sample stimulus. Details are as in Fig. 1. For subject J2, three data points (indicated by broken lines) lie below 40% correct responses. The actual values of these data points, reading from left to right, are 25%, 25%, and 17%.

sion (pilot data indicated that each drug was behaviorally active at this presession injection interval). Doses studied, selected on the basis of previous reports and pilot data from our laboratory, were: chlorprothixene (4, 6, 8, and 10 mg/kg), haloperidol (0.13, 0.25, 0.38 and 0.5 mg/kg), and trifluoperazine (0.5, 1, 2, and 3 mg/kg). Each bird received each dose of every drug on two occasions in an irregular order that varied across subjects.

RESULTS

In general, during control sessions accuracy (percent correct responses) decreased with increases in delay interval and saline injections did not affect performance. Figures 1, 2, and 3 respectively show the effects of chlorprothixene, haloperidol, and trifluoperazine on percent correct responses at each of the five delay values and rate of responding (responses/min) to the center key while illuminated.

At higher doses, chlorprothixene generally decreased accuracy at all delay values. In two of three subjects (J1, J2), the accuracy-decreasing effects of chlorprothixene were generally dose-dependent, and in all subjects the magnitude of the drug-induced decrease in accuracy was greatest at the longest delay values. The effects of chlorprothixene on reponse rate varied across subjects. Drug-induced rate increases were observed in subjects J1 and J3. The response rate of subject J2, in contrast, was below the control value at the three highest doses of chlorprothixene.

Haloperidol did not consistently impair accuracy at any delay value. Rather, percent correct responses when haloperidol was given typically approximated control values at the three shortest delay values and, in 17 of 24 instances, exceeded control values at the two longest delays. Haloperidol produced dose-dependent decreases in the rate of responding of subjects J1 and J3, and inconsistently affected the response rate of subject J2.

Trifluoperazine produced generally dose-dependent decreases in percent correct responses for subjects J2 and J3, but little affected the accuracy of subject J1. For those subjects whose accuracy was impaired by the drug, the magnitude of the effect typically was greatest at the longest delay intervals. The lowest dose of trifluoperazine was associated with an increased rate of responding by subject J1. In all other instances, response rate was reduced by the drug relative to control values, with the magnitude of this effect being generally dose-dependent.

In those instances where a drug reduced the rate of responding to the center (sample) key, the number of trials completed typically decreased relative to control values. This effect is evident in Table 1, which shows the number of

TABLE 1

NUMBER OF TRIALS COMPLETED BY EACH BIRD UNDER ALL EXPERIMENTAL CONDITIONS*

	Chlorprothixene (mg/kg)				
Pigeon	0	4	6	8	10
J1	280	280	280	280	269
J2	280	280	172	276	155
J3	280	280	154	280	280
	Haloperidol (mg/kg)				
Pigeon	0	0.13	0.25	0.38	0.5
J1	280	246	178	162	109
J2	280	280	280	280	240
J3	280	162	221	172	143
	Trifluoperazine (mg/kg)				
Pigeon	0	0.5	1	2	3
J1	280	280	214	232	197
J2	280	221	70	59	75
J3	280	275	197	62	118

*Drug data represent the total number of trials completed during the two sessions in which a particular dose was given. Control data represent the mean number of trials completed during individual predrug control sessions, times two.

trials completed by each bird under all experimental conditions.

Overall effects of individual drugs did not vary as a function of sequence of administration and, within drugs, the effects of first and second administrations of a particular dose did not systematically differ. This suggests that, although neuroleptics were given repeatedly in the present study, neither supersensitivity nor tolerance occurred.

DISCUSSION

Previous reports of the effects of neuroleptic drugs under matching-to-sample procedures are few. In monkeys, the phenothiazine chlorpromazine has been shown to interfere with performance under matching-to-sample procedures in which delays are [5,11] and are not [10] arranged between the offset of the sample stimulus and the onset of the comparison stimuli. Another phenothiazine, thioridazine, also has been found to interfere with the accuracy of mentally retarded humans exposed to a DMTS procedure [13]. Results of these earlier reports, which suggest that phenothiazines deleteriously affect performance under the DMTS procedure at doses that do not strongly suppress responding, are consistent with the present observation that the phenothiazine trifluoperazine generally impaired pigeons' accuracy in performing a DMTS task.

The thioxanthene tested in the present study, chlorprothixene, typically reduced accuracy under the DMTS procedure. Haloperidol, a butyrophenone, failed to do so even at doses that strongly decreased rate of responding to the sample stimulus. No previous investigations have examined the effects of thioxanthenes under matching-to-sample procedures, and only one has examined the effects of butyrophenones under such procedures. In that study [2], relatively high doses of haloperidol were found to interfere with monkeys' DMTS performance. However, "although significant impairments in delayed-response accuracy were observed with the higher doses of haloperidol, this impairment was unrelated to the duration of the retention interval, implying a more general, non-mnemonic dysfunction" ([2], p. 353). Such general drug-induced behavioral dysfunction may have accounted for the rate reductions observed when haloperidol was given in the present study, although these reductions were not accompanied by a reduction in the accuracy of matching.

While no investigations have directly compared the effects of different neuroleptics under the DMTS procedure, various neuroleptics have been demonstrated to have dissimilar profiles of action in other assays. For example, in pigeons keypecking under a multiple fixed-ratio 30 fixed-interval 5-min schedule of food delivery, chlorprothixene "decreased responding relatively more within the fixed-interval component than within the fixed-ratio component and also produced rate-dependent effects within the fixed-interval component" ([8], p. 689). In contrast, trifluoperazine and haloperidol "also decreased responding relatively more within the fixed-interval component than within the fixed-ratio component, but did not produce rate-dependent effects within the fixed-interval component" ([8], p. 689).

Chlorpromazine and haloperidol also have been found to have different effects on pigeons' performance under a fixed-consecutive-number schedule, where a reinforcer (food) was delivered dependent on the emission of at least eight consecutive responses on one key, followed by a single response on (i.e., a switch to) a second key [7]. Under this schedule, chlorpromazine was associated with an increase in premature switching, regardless of whether an exteroceptive stimulus signalled completion of the initial ratio requirement (i.e., emission of eight consecutive responses on the appropriate key). Haloperidol was not associated with premature switching, although like chlorpromazine it produced dose-dependent decreases in overall response rate. These findings, like those of the present study, suggest that haloperidol does not strongly affect responding in tasks involving recent memory, although other neuroleptics (e.g., chlorpromazine, chloprothixene, trifluoperazine) may do so under similar conditions. This conclusion is of potential clinical significance given that the various neuroleptics do not clearly vary with respect to their ability to reduce psychotic behaviors [1], which renders side effects a major consideration in their selection. Interference with short-term memory is surely a significant side effect. If future research with humans confirms that various classes of neuroleptics or specific agents differ with respect to their memory-disrupting actions, this side effect certainly should be considered in choosing a therapeutic agent.

REFERENCES

1. Baldessarini, R. J. Drugs and the treatment of psychiatric disorders. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, edited by A. G. Gilman, L. S. Goodman and A. Gilman. New York: MacMillan, 1980, pp. 391–447.

2. Bartus, R. T. Short-term memory in the rhesus monkey: Effects of dopamine blockade via acute haloperidol administration. *Pharmacol Biochem Behav* 9: 353–357, 1978.

3. Berryman, R., M. E. Jarvik and J. A. Nevin. Effects of pentobarbital, lysergic acid diethylamide and chlorpromazine on matching behavior in the pigeon. *Psychopharmacologia* **3**: 60–65, 1962.
4. Davis, J. M. and D. L. Garver. Neuroleptics: Clinical use in psychiatry. In: *Handbook of Psychopharmacology*, vol 10, edited by L. L. Iverson, S. D. Iverson and S. B. Snyder. New York: Plenum Press, 1978, pp. 129–164.
5. Glick, S. D., T. L. Goldfarb, F. Robustelli, A. Geller and M. E. Jarvik. Impairment of delayed matching in monkeys by chlorpromazine and pentobarbital. *Psychopharmacologia* **15**: 125–133, 1969.
6. Hollister, L. E. *Clinical Pharmacology of Psychotherapeutic Agents*. New York: Churchill-Livingstone, 1978.
7. Laties, V. G. The modulation of drug effects on behavior by external discriminative stimuli. *J Pharmacol Exp Ther* **183**: 1–13, 1972.
8. Leander, J. D. Rate-dependent effects of drugs. II. Effects of some major tranquilizers on multiple fixed-ratio, fixed-interval schedule performance. *J Pharmacol Exp Ther* **193**: 670–689, 1975.
9. Picker, M. and A. Poling. Choice as a dependent measure in autoshaping: Sensitivity to frequency and duration of food presentation. *J Exp Anal Behav* **37**: 393–406, 1982.
10. Pragay, E. B., A. F. Mirsky and J. M. Abplanalp. The effects of chlorpromazine and secobarbital on matching from sample and discrimination tasks in monkeys. *Psychopharmacologia* **16**: 128–138, 1969.
11. Scheckel, C. L. *The Effect of Chlorpromazine (Thorazine) and Chlordiazepoxide (Librium) on Delayed Matching Responses in the Macaca mulatta*. Doctoral dissertation, Fordham University, 1963.
12. Thompson, D. M. Stimulus control and drug effects. In: *Contemporary Research in Behavioral Pharmacology*, edited by D. E. Blackman and D. J. Sanger. New York: Plenum Press, 1978, pp. 159–207.
13. Wysocki, T., W. Fuqua, V. J. Davis and S. E. Breuning. Effects of thioridazine (Mellaril) on titrating delayed matching-to-sample performance of mentally retarded adults. *Am J Ment Defic* **85**: 539–547, 1981.