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Titrating Matching-to-Sample Performance: Effects of Drugs of Abuse and Intertrial Interval

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WENGER, G. R. AND K. A. KIMBALL. *Titrating matching-to-sample performance: Effects of drugs of abuse and intertrial interval.* PHARMACOL BIOCHEM BEHAV **41**(2) 283–288, 1992.—Previous reports have shown that increasing the length of the intertrial interval (ITI) in a matching-to-sample schedule of reinforcement results in increased matching accuracy. This has traditionally been interpreted in the context of proactive inhibition, the disruption of memory for a stimulus as a consequence of events that occurred prior to the presentation of the stimulus. In an effort to more fully characterize a titrating matching-to-sample baseline, the effect of ITI ranging from 0–30 s was determined in pigeons trained to respond under the titrating matching-to-sample procedure. In addition, the effect of ITI length on the dose-response curve for pentobarbital, phencyclidine, D-amphetamine, and cocaine were determined. Surprisingly, performance under the titrating matching-to-sample was not altered as a function of ITI length, nor did the effects of the four drugs of abuse change as a function of ITI length. These results suggest that performance under the titrating matching-to-sample is under a different control than matching-to-sample using fixed delays.

Matching-to-sample Titration schedule Pigeon Proactive interference
Cocaine Phencyclidine D-Amphetamine Pentobarbital

DELAYED matching-to-sample has been widely used in the study of short-term memory in laboratory animals. In a pigeon or monkey, the usual procedure involves presenting a sample stimulus on the center key or lever of a three-key/lever operant panel. Following the presentation of the sample stimulus for either a fixed period of time or until a specified number of responses has been made on the lever or key associated with the stimulus, the sample stimulus is extinguished and a delay follows. Upon completion of the delay, two or more stimuli are presented, one of which is identical to the sample stimulus presented prior to the delay. A response on the lever/key associated with the stimulus that "matches" the sample stimulus results in access to food. An intertrial interval of some specified length may or may not separate each trial.

Although this procedure appears relatively straightforward as a measure of short-term memory, in the absence of drug administration accuracy has been shown to be influenced by a number of variables [for reviews, see (9,13)]. For example, accuracy is affected by the length of presentation of the sample stimulus (5,8), the number of responses required to extinguish the sample stimulus (6), the length of the delay (5,6), whether the delay length is fixed or whether it changes as a function of the subject's performance accuracy (1,12,15), the degree of illumination during the delay (4), the length of the intertrial interval (2,5,7,10), and the amount of illumination present during the intertrial interval (2). Thus, short-term memory would appear to be influenced by the procedural variables employed.

While changing any one of these variables can be shown to alter the subject's matching performance, it also has been shown that there is interaction among some of the variables. To illustrate, Nelson and Wasserman (5) showed that percent accuracy of the matching performance in pigeons increased as the exposure time to the sample stimulus was increased, or as the delay interval was decreased, or as the intertrial interval (ITI) increased. In addition, pigeons given a longer exposure time to the stimulus and a shorter delay interval performed at a higher percent matching accuracy than that observed with just a short delay interval and a short stimulus presentation. Similarly, pigeons given a longer ITI and a shorter delay performed at a higher matching accuracy than pigeons exposed to just a shorter delay or just a longer ITI.

A significant problem associated with using the traditional matching-to-sample procedure with a fixed-delay value is the

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use of percent correct as the dependent variable. Typically, the subject is trained to some level of stability of the behavioral response prior to drug or experimental modification. Unfortunately, this is frequently associated with a high percentage of accuracy that will not allow for significant improvement above the baseline accuracy. In addition, with two stimuli presented chance performance is defined by 50% accuracy of the matching response. Thus, a rather prominent "ceiling" and "floor" limit the range of effects produced by drug administration or experimental manipulation. Consequently, a titration procedure (15), in which the length of the delay is adjusted to achieve an overall accuracy rate of approximately 80%, is currently in use in this laboratory. Using this procedure, the length of the delay can be plotted as the dependent variable rather than percent accuracy. Specifically, the mean delay value achieved during the experimental session has been shown to be a reliable indicator of overall session performance (15). The use of the mean delay value as the dependent variable rather than percent correct minimizes the ceiling and floor effects observed with the use of percent correct.

Although there exists a significant amount of data reporting how various procedural variables alter short-term memory, there is a surprisingly smaller database on drug effects on short-term memory as measured by the delayed matching-to-sample procedure. There is even less information available on how drug administration modulates the role of the various procedural variables in determining matching performance. Consequently, the purpose of this study was twofold: to determine how changes in the ITI would affect matching performance using a titrating delay value and to determine how changes in the ITI would interact with effects of drugs of abuse on matching accuracy.

METHOD

Subjects

Subjects were five adult, male, White Carneau pigeons (Palmetto Pigeon Plant, Sumter, SC). Body weights of the pigeons were reduced to 80% of the free feeding weight and maintained at this weight throughout the course of the experiment by postsession feeding. Pigeons were individually housed and given free access to water, except during experimental sessions. They were maintained under a 12 L:12 D cycle (lights were on from 0700–1900 h). All subjects had previous training under a titrating matching-to-sample procedure with an ITI set at 0, and all subjects had been previously tested after administration of a variety of drugs.

Apparatus

Subjects were trained and tested in standard pigeon chambers (Model no. G7313; Ralph Gerbrands Co., Arlington, MA) that contained three response keys, each of which could be transilluminated with white, red, or green lights. The chamber was housed in a sound- and light-attenuating enclosure (Model no. G7211; Ralph Gerbrands Co.). Below the center key of the operant chamber, a feeder trough was located. Opening of the response-key contacts defined the response and operated a relay mounted inside the enclosure producing auditory feedback upon a response. A force of 0.15 N was required to open the key contacts. Responses on the keys were recorded by microprocessor equipment (TRS-80, Model III; Tandy Corp.) located in the adjacent room. Two 28-V DC light bulbs (No. 1819) provided illumination inside the enclosure at all times except during the presentation of food and during time-out periods.

Schedule

Training of the pigeons under the titrating matching-to-sample schedule has been described earlier (15). Under the final schedule, each trial began with illumination of the center key in the chamber, which was randomly assigned a green or red color. Responding on this center key under an FR15 schedule of reinforcement (observation phase) turned off the center key light and initiated a delay period during which all key lights were extinguished. After a delay of at least 3 s, two of the three response keys were transilluminated, one red and the other green. Which two of the three keys were illuminated on a given trial varied randomly among the left, center, and right response keys. A single response on the key transilluminated with the same color presented during the observation phase (matching response) was defined as a correct response and resulted in a 5-s access period to Purina pigeon checkers. A response on the key transilluminated with the color not presented during the observation response was defined as being incorrect and produced a 5-s time-out period during which all lights in the chamber were extinguished. Each trial was followed by a time-out period (ITI) during which no stimuli were presented and the chamber was darkened. Dose–response curves were first determined for each drug with an ITI of 0 s. Following the completion of the dose–response curves, the schedule was changed such that the ITI equaled 10 s, the behavior was allowed to stabilize at the new ITI value, and the dose–response curves were redetermined. The final phase of the experiment involved changing the ITI to 30 s, allowing the behavior to once again stabilize, and a final determination of the drug effects.

Sessions continued for 50 trials or 1 h, whichever occurred first. The maximal 1-h session length excluded intertrial intervals and matching-to-sample delay periods. The delay value remained at 3 s for the first five trials, after which it was reset for each subsequent trial based upon the following criteria: If a correct matching response was made in five of the five previous trials, the delay value was increased by 3 s; if four of the five previous matching responses were correct, the delay value remained at its previous level; if three or less of the previous five matching responses were correct, the delay value decreased by 3 s, to a minimum of 3 s.

Data Analysis

For each session, the following values were calculated: the mean delay value across all trials, the rate of responding during the completion of the FR15 on the observation (center) key, the percentage of correct matching responses, and the response latency to the choice stimuli. The rate of responding was calculated by dividing the total number of observation responses on the center key by the total time required to complete the FR15. In addition, the latency to respond to the choice stimuli was totaled for the entire session. A mean latency value was then calculated by taking the total latency time and dividing by the number of trials in the session.

In presenting group data for the effects of the drugs of abuse on the mean delay, a given subject was excluded from the group mean if it failed to complete at least 10 trials in a given session. A conservative estimate of the standard error of the means for control values was calculated by dividing the

total standard deviation (n-1) of the individual control values from all control sessions by the square root of the number of subjects.

Drugs

Na pentobarbital, D-amphetamine SO_4, and cocaine HCl were obtained from Sigma Chemical Co. (St. Louis, MO). Phencyclidine HCl was obtained from the National Institute on Drug Abuse (Bethesda, MD). All drugs were dissolved in 0.9% saline, and doses were calculated and are expressed as the respective salts. Drug treatments were given on Tuesdays and Fridays, with Thursdays serving as saline control sessions. Injections were administered into the breast muscle in a volume of 1 ml/kg body weight 5 min prior to the start of the operant sessions.

RESULTS

Under control conditions, the titration schedule continually adjusted the length of the delay such that an overall session accuracy of approximately 80% was achieved in all five pigeons. To achieve this, the delay increased significantly from the starting value of 3 s for all five pigeons. In pigeon P182, the maximum delay rose to an average of 45 s, while in pigeon P236 the average maximum delay rose to 21 s (data for maximum delay values not shown). The mean delay for the session provided a reliable indicator of matching accuracy in all five pigeons and ranged from approximately 9 s (P236) to 20 s (P182 and P25).

There was very little difference in control performance as a function of the length of the ITI (Fig. 1). Although there was considerable variation between subjects in the mean delay value, for an individual pigeon the mean delay value for the session did not change as a function of ITI length (Fig. 1, upper left panel). Since the delay value on the sixth and all subsequent trials was determined by the accuracy of the matching performance on the previous five trials, and neither the mean delay nor the maximum delay (data not shown) values achieved for the session changed as a function of ITI length, it is clear that the matching accuracy was not influenced by the length of the ITI. Thus, overall accuracy for the session did not change as a function of the ITI length (Fig. 1, lower left panel). Likewise, neither the rate of responding (Fig. 1, upper right panel) nor the latency to respond to the choice stimuli (Fig. 1, lower right panel) changed as a function of the length of the ITI. This is true in spite of large differences in the control rate of responding in individual pigeons. P25 and P182 had the lowest rate of responding (0.13-0.22 res/s) and P236 had the highest rate of responding (1.8 res/s).

To more fully explore the role of the length of the ITI on matching performance, the effects of four drugs of abuse were determined at each ITI value. Pentobarbital (Fig. 2) produced a nearly identical effect at each of the three ITI lengths. Under all three conditions, pentobarbital decreased the mean delay value at doses of 5.6 and 10 mg/kg. The decrease in the mean delay value was the result of a decreased matching accuracy, and the titration schedule reduced the length of the delay to a value that would allow the pigeons to perform at 80% accuracy. Interestingly, this effect was not the result of a general suppression of function since rate of responding was increased at doses of 3, 5.6, and 10 mg/kg. There were no differences in the effects of pentobarbital on the mean delay or rate of responding as a function changes in ITI length.

The effect of phencyclidine on matching performance was characterized by a dose-related decrease in the mean delay value (data for phencyclidine not shown). Although the effect was observed over a narrower dose range than that observed with pentobarbital, phencyclidine also demonstrated a degree of specificity in its effect on matching accuracy. The mean delay value was decreased under all three ITI values at a dose of 1 mg/kg, a dose that had no effect on rate of responding.

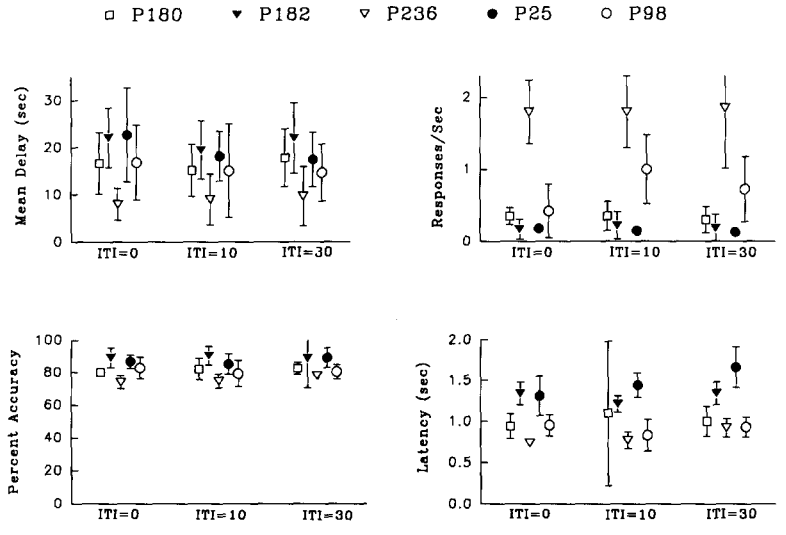

FIG. 1. Effect of changes in the length of the ITI on the performance of pigeons responding under the titrating matching-to-sample baseline. Abscissa, length of the ITI in seconds; ordinate (top left), mean delay achieved for the session in seconds; ordinate (top right), rate of responding in res/s; ordinate (lower left), overall percent accuracy of matching responses; ordinate (lower right), latency in seconds to respond to the choice stimuli following the delay. Points and brackets represent the mean ± SD of a minimum of 15 saline determintions in each pigeon.

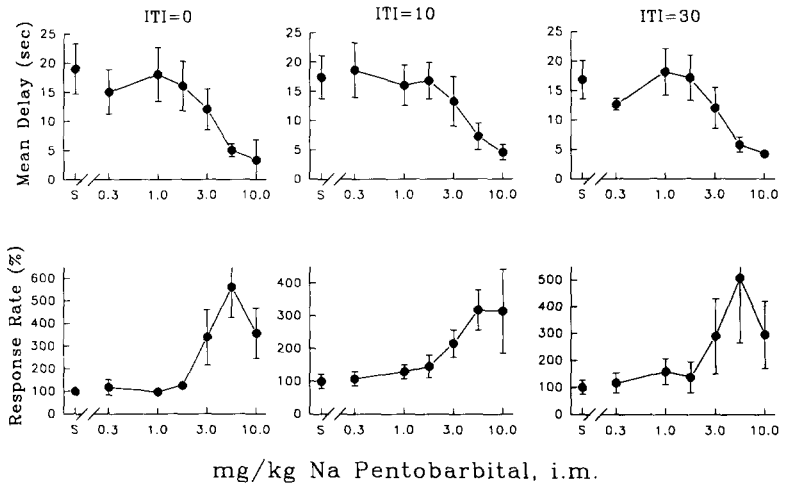

FIG. 2. Effect of Na pentobarbital on matching performance at the three different ITI lengths. Abcissa, dose in mg/kg on a log scale; ordinate (top), mean delay achieved for the session in seconds; ordinate (bottom), rate of responding as a percentage of control. Points and brackets above S represent the mean ± SE following saline administration. Data points for the effects of pentobarbital represent the mean ± SE of single determinations in each of the five pigeons.

At 3 mg/kg, the rate of responding was suppressed to the point that only one pigeon completed a sufficient number of trials to permit a determination of the mean delay value at ITI values of 0 and 30 s. No pigeon completed enough trials at an ITI of 10 s to permit a determination of the mean delay value. Thus, as with pentobarbital, the effects of phencyclidine did not change as a function of ITI value.

The effect of D-amphetamine on matching accuracy was also determined under all three ITI conditions (Fig. 3). Unlike pentobarbital and phencyclidine, over the dose range studied D-amphetamine had minimal effects on the mean delay value even up to doses that clearly produced effects on rate of responding. Under all three ITI conditions, rate of responding was markedly suppressed following the 3 mg/kg dose. A dose of 1 mg/kg increased the rate of responding when ITI equaled 0 s, but this effect was not observed at longer ITI values.

Similarly, cocaine, unlike pentobarbital and phencyclidine, only affected the mean delay value at doses that produced marked decreases in rate of responding. With ITI values of 0 and 30 s, decreases in the mean delay values were observed following 5.6 and 10 mg/kg cocaine. These doses were associated with marked decreases in response rate, and only a minority of the pigeons completed enough trials to allow a determination of the mean delay value. When the dose-response curves were determined at an ITI value of 10 s, there was no

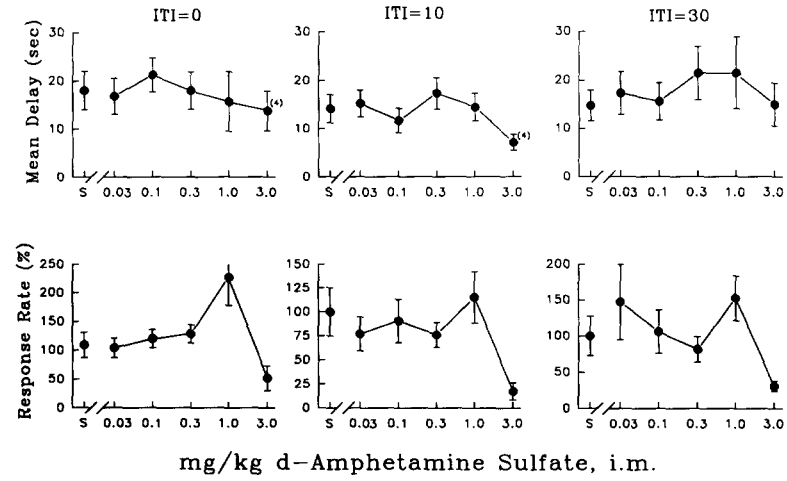

FIG. 3. Effect of D-amphetamine SO_4 on matching performance at the three different ITI lengths. Data presented as in Fig. 2. Where animals have been excluded from the calculation of the mean due to response suppression, the number of animals contributing to the mean is indicated by (*n*).

decrease observed in the mean delay value even in the one pigeon that completed enough trials at 10 mg/kg to allow for a determination of rate of responding. It also should be noted that in the one pigeon (P182) that completed enough trials to allow for a determination of a mean delay value at 10 mg/kg the rate of responding was reduced to 40% of his control rate. Thus, even in this pigeon, cocaine failed to disrupt matching accuracy and affect the mean delay value at doses lower than those required to decrease the rate of responding.

DISCUSSION

Numerous investigators have reported that in pigeons responding under a delayed matching-to-sample schedule of reinforcement increasing the length of the ITI is associated with increased accuracy of matching performance (2,4,5,7,10). This improvement of matching accuracy as a function of increased ITI length has generally been interpreted in the context of proactive inhibition, the disruption of memory for a stimulus as a consequence of events that occurred prior to the presentation of the stimulus. Thus, in the delayed matching-to-sample situation an example of proactive inhibition would be the disruption of matching performance on trial *n* by the events of trial *n*-1. Increasing the ITI in a delayed matching-to-sample baseline results in a separation of trial *n* and *n*-1 and is thought to minimize the interaction between the two events. Consequently, short ITI's increase the probability that the events of trial *n*-1 will interfere with the performance on trial *n*, and long ITI's decrease the probability that the events of trial *n*-1 will interfere with performance on trial *n* [for a recent review, see (13)]. Thus, the failure to see an effect in control performance in this experiment, in any direction, as a result of changes in the ITI ranging from 0–30 s was quite surprising. No effect of ITI length was observed in the accuracy of matching performance as indicated by changes in the mean delay value, rate of responding, or choice-key latency. Most reports indicate that for pigeons no further improvement in matching accuracy is associated with an ITI in excess of 20–25 s (2,3,5,7). Thus, the failure to see an effect in these experiments cannot be related to a failure to explore a wide enough range of ITI's. Possible explanations for the failure to see an effect of changes in the length of the ITI include: the degree of illumination of the chamber during the ITI, the longer delay values reported in the present experiment compared to many experiments that have examined the effect of ITI length on matching performance, and the titration schedule itself.

Previous workers (2,11) have shown that the degree of illumination during the ITI is an important variable capable of modifying the relationship between the length of the ITI and matching performance. In both reports, matching accuracy of pigeons decreased with increasing ITI duration when the chamber was illuminated during the ITI. This is exactly the opposite of what is reported when the ITI period is spent in darkness (2,7,10). Thus, based upon the literature, one would have predicted that since the ITI in the present experiment was spent in darkness an increase in matching accuracy (longer mean delay values) with increasing ITI length should have been observed. Consequently, it is unlikely that the degree of illumination in the chamber during the ITI is the explanation for a failure to observe an effect of the ITI length.

A more plausible explanation for the failure to observe an effect of increasing ITI length is the length of the delay achieved by the pigeons under the titration schedule. The length of the delay achieved by the pigeons responding under the titrating schedule was much longer than what is usually reported for pigeons responding under a matching-to-sample baseline. It should be remembered that the delay value under the titrating schedule started at 3 s, and the pigeons regularly pushed this value to exceedingly long values. Several pigeons averaged maximum delays of greater than 35 s and one pigeon (P182) had a maximum delay that averaged in excess of 40 s. As a result, even the average delays for a session were longer than the delays studied with pigeons in most studies. The mean delays for the pigeons in this study ranged from approximately 9 s (P236) to approximately 20 s (P182 and P25). In light of this, it is interesting that Grant (3) reported that the proactive interference observed in pigeons was greatest when the delay values and ITI were short, and the degree of interference appeared to decline at longer delay values and longer ITI's. Using a 2-s ITI, a large interference effect was observed at delay values ranging from 2–6 s. However, the apparent interference decreased at delay values ranging from 6–10 s. Grant postulated that the strength of the memory of the stimulus from trial *n*-1 declined significantly over the longer delay values, and by 10 s the memory of the stimuli from trial *n*-1 no longer provided any significant interference during the choice following a 10 s delay on trial *n*. If this is the case, then it is reasonable to assume that with the longer delays observed under the titration schedule very little proactive interference should be observed. Thus, changes in the length of the ITI should result in minimal changes in performance accuracy.

The titration schedule itself must also be considered as a significant variable. Matching accuracy under the titration schedule occurred at a higher level of accuracy and at longer delay values than those usually reported in experiments using fixed-delay values. What it is about a titration baseline that results in this improved performance is not known. However, it is quite clear that the matching performance is different and, therefore, it must be presumed that the control of the behavior is also different in some way. Thus, the possibility that the previously reported relationships between proactive interference and the length of the ITI may not hold for the titration baseline. Future experiments will be required to determine the exact reasons for the observations reported here.

To the authors' knowledge, drug effects on proactive interference have not been widely studied. The drugs selected for study here were based upon previous work in this laboratory on drugs of abuse (15). Pentobarbital and phencyclidine were shown to have rather specific effects on matching performance at doses that either increased or had no effect on rate of responding. In contrast, D-amphetamine and cocaine were reported to affect matching accuracy at doses that markedly decreased rates of responding. This study replicated the earlier findings on the effects of these drugs on titrating matching performance and extended the results to examine the effect of different ITI's on the drug effects. In this regard, it is interesting that changes in ITI length failed to modify the effect of any of the four drugs on matching performance. Whether this failure to see changes in the effects of these drugs as a function of ITI length is specific to these drugs or the titration schedule is not known. The drugs studied here were selected because they either had been previously shown to have very specific effects on matching accuracy (matching accuracy was decreased without decreasing response rate) or had been shown to have no effects on matching accuracy at doses that did not markedly suppress responding (15). As part of a different study, scopolamine and physostigmine were studied in these same pigeons at ITI values of 10 and 30 s and no differences were observed as a function of ITI length (14). Thus, the

failure to see an effect of ITI length across a fairly wide range of pharmacological classes would argue against the possibility that the failure to see an effect is due to the drugs studied. Therefore, the failure to see an effect of ITI length following drug administration may be, as in the control condition, related to the titration schedule. It is interesting, however, that even though the titration schedule appears to be relatively insensitive to proactive interference, as determined by changes in the length of the ITI, the behavior maintained by the schedule is easily disrupted by pharmacological agents in rather specific ways.

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