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Benzodiazepine-Induced Impairment of Matching-to-Sample Performance in Humans[1]

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ROACHE, J. D., D. R. CHEREK, R. SPIGA, R. H. BENNETT, K. A. COWAN AND J. YINGLING. *Benzodiazepine-induced impairment of matching-to-sample performance in humans*. PHARMACOL BIOCHEM BEHAV 36(4) 945–952, 1990.—The effects of benzodiazepines on a visual pattern matching-to-sample (MTS) task were examined in nine healthy male volunteers. The MTS task employed randomly generated checkerboard-like stimuli presented on a video display. The sample and two comparison stimuli were simultaneously presented. Nonmatching comparison stimuli were randomly generated to be 3.125, 6.25, 12.5, 25.0, 37.5, or 50.0 percent different from the sample. Subjects responded on left or right button manipulanda to identify the matching comparison stimulus. The nonmatching stimulus condition was maintained constant for a 60-sec component and the percentage difference of the nonmatching stimuli was systematically varied across multiple components. The effects of triazolam (2.25–9.0 μg/kg) and lorazepam (7.5–45 μg/kg) were examined in a within-subjects, double-blind, placebo-controlled study. Under placebo conditions, response rates and accuracy were a positive function of the nonmatching stimulus discriminability. Triazolam produced dose-related decreases in response rate at nonmatching stimulus conditions ≥25%. Only the 9.0 μg/kg dose of triazolam decreased accuracy and this occurred across all nonmatching stimulus conditions. Lorazepam effects were qualitatively similar but less robust than those of triazolam.

Matching-to-sample Benzodiazepines Humans Performance Triazolam Lorazepam Stimulus control Stimulus discrimination

MATCHING-TO-SAMPLE (MTS) procedures have been used to examine the manner in which environmental stimuli control behavior (15,22). The basic MTS paradigm usually involves the presentation of a sample stimulus simultaneous with the presentation of two or more comparison stimuli, one of which is identical to (i.e., matches) the sample stimulus. Responses associated with the matching comparison stimulus are reinforced while nonmatching responses are not. Stimulus control is achieved when subjects accurately respond to the matching stimulus. One variation of the MTS procedure involves the introduction of time delays between the presentation of the sample and the subsequent presentation of comparison stimuli. These "delayed-MTS" procedures have been used to study short-term memory operationally defined as sample stimulus control of the matching response in the temporal absence of the sample stimulus (8).

Previous studies have used delayed-MTS procedures to examine the effects of CNS depressants on stimulus control and memory processes. Barbiturates have been shown to decrease delayed-MTS accuracy and response rate in pigeons (1,8) and monkeys (11). Benzodiazepines also have been shown to decrease delayed-MTS accuracy and response rate in pigeons (9, 13, 14) and monkeys (10). In those delayed-MTS studies which varied the length of the delay interval, benzodiazepines (10) but not barbiturates (1, 8, 11) were found to interact with the length of the delay such that greater reductions in accuracy were observed at the longer delay intervals. Using simultaneous MTS procedures without delay intervals, pentobarbital has been reported to decrease MTS performance accuracy (1,2); however, the effects of benzodiazepines have not been examined. Both simultaneous and delayed-MTS performance have been examined in humans (15, 19, 20, 23). However, the effects of CNS depressants on human MTS performance have not been examined.

MTS and delayed-MTS studies typically have employed a few readily discriminable stimuli which are repeatedly presented over

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a fixed number of trials so that the primary dependent measure is response accuracy (22). Although not strictly an MTS paradigm, stimulus generalization procedures have quantitatively varied stimuli along some dimension (e.g., light wavelength) and then tested the discriminability or generalizability of these stimuli to the original discriminative stimulus (5). These studies have uniformly reported that the probability of responding is a positive function of the similarity of the different stimulus to the original discriminative stimulus.

The present study examined the effects of two benzodiazepines, triazolam (TZ) and lorazepam (LZ), on MTS performance in humans. The MTS task is a newly developed procedure which combines several features of the basic MTS and stimulus generalization paradigms. In this procedure, unique sets of randomly generated checkerboard-like visual pattern stimuli were used as sample and comparison stimuli presented on a computer video screen. The degree of difference between the matching and nonmatching comparison stimuli was systematically varied and dose-response functions for each drug were assessed. This research represents an initial attempt to examine the usefulness of MTS procedures in an analysis of performance deficits produced by widely used psychotropic drugs.

METHOD

Subjects

Nine male volunteers participated; four black, four white and one Hispanic. Subjects ranged in age from 19–41 years (mean = 29), and in education from 12–16 years (mean = 12.8); body weights are listed in Table 1. Subjects were normal and healthy as determined by physical exam, brief psychiatric interview, and structured interviews using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) (21) and a lifetime frequency/amount drug history questionnaire. No subject had histories of psychiatric disorder according to the criteria specified in the Diagnostic and Statistical Manual of the Mental Disorders (DSM III-R) (4). Five subjects were smokers (mean = 18 cigs/day) and seven were regular caffeine users (mean = 221 mg/day). All subjects had alcohol experience with four subjects reporting infrequent use (≤1 drink/month), one subject (S344) reporting regular use of 3 drinks/day, and four subjects reporting mainly weekend use of 4–24 drinks/month. Subjects were instructed not to eat solid foods or drink caffeine containing beverages in the morning before reporting to the laboratory. Upon reporting each day, subjects were required to provide alcohol-free breath samples and drug-free urine samples. Daily breath samples were tested with an Alco-Sensor III (Intoximeters, Inc.) and approximately one-third of the urine samples were tested using an EMIT-d.a.u. assay system capable of detecting all major classes of drugs of abuse as well as major classes of prescription and nonprescription psychotherapeutic agents. All breath and urine samples tested from those experimental days reported in this paper were drug-free.

Daily Procedure

Subjects reported to the laboratory three days each week (M,W,F) for at least 15 experimental sessions. Sessions began at 0815 hr and subjects were required to remain in the laboratory until 1615 hr. All drugs or placebo were administered at 0930 hr. Subjects completed a series of performance tests and questionnaires repeatedly throughout the session. Testing began with the matching-to-sample (MTS) task and was followed by the subject-rated questionnaires. These tests took approximately 22 min and 3 min to complete, respectively, and were begun at 0845 hr (i.e., predrug) and at 0.5, 1.5, 3.0, 4.5 and 6.0 hr following drug administration. At selected times, subjects also completed a computerized digit-symbol-substitution task (DSST) and a number recall task (data not reported). These tests took approximately 6 min and were completed at 0915 hr (predrug) and at 2.0, 3.5 and 5.0 hr following drug administration. Subjects were paid daily earnings dependent upon their MTS performance and also received additional accumulated earnings upon completion of the entire experiment.

TABLE 1

SUBJECT TREATMENT CONDITIONS

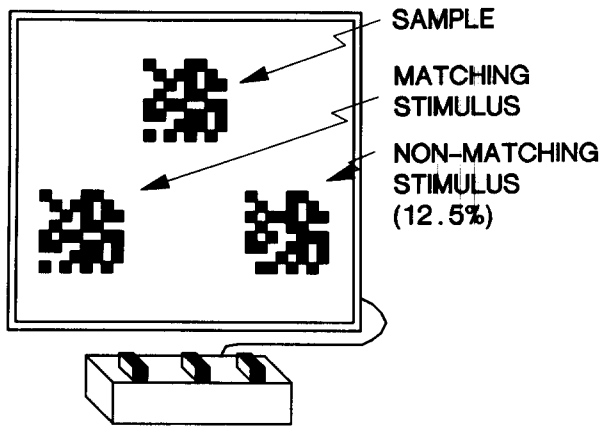
Subject	Weight (kg)	Drug Sequence	Triazolam Doses (μg/kg)	Lorazepam Doses (μg/kg)
S326	79.55	TZ, LZ	2.25, 4.5, 9.0	7.5, 15.0, 30.0
S334	63.49	LZ, TZ	2.25, 4.5, 9.0	7.5, 15.0, 30.0
S344	61.22	LZ, TZ	2.25, 4.5, 9.0	7.5, 15.0, 30.0
S350	58.96	TZ, LZ	2.25, 4.5, 9.0	7.5, 15.0, 30.0
S378	70.29	TZ, LZ	2.25, 4.5, 9.0	7.5, 15.0, 30.0
S398	85.71	LZ, TZ	2.25, 4.5, 9.0	7.5, 15.0, 30.0
S419	86.17	TZ, LZ	2.25, 4.5, 9.0	11.25, 22.5, 45.0
S406	66.67	LZ only	none	11.25, 22.5, 45.0
S412	68.03	LZ only	none	11.25, 22.5, 45.0

Drugs

All drugs or placebo were administered orally in two opaque, size 0 gelatin capsules at 0930 hr under double-blind conditions. TZ (triazolam: Halcion, The Upjohn Co.) and LZ (lorazepam: Ativan, Wyeth Laboratories) doses were administered per kg of subject body weight. Drug doses (see Table 1) were prepared by mixing corn starch with whole and crushed partial tablets combined to deliver the required dosage. Placebo capsules contained only corn starch. TZ doses were 2.25, 4.5 and 9.0 μg/kg. For six subjects, LZ doses were 7.5, 15.0 and 30.0 μg/kg and in three subjects, the doses were increased by 50%. No capsules were ingested on the first experimental day and placebo was administered on days 2–5 to allow for acclimation and practice with experimental procedures. Beginning on day 6 (except for S344 who began on day 5), doses of TZ or LZ were administered in an ascending series. The order of TZ and LZ administration was counterbalanced across subjects (Table 1) and at least one placebo day occurred between the two different drugs for those subjects who received both.

Matching-to-Sample (MTS) Apparatus

The MTS task utilized an Apple II-GS computer with a black background monochrome monitor. "Checkerboard"-like visual stimulus patterns were created by randomly highlighting 32 of the 64 little squares created from an 8 × 8 square matrix; the final video display pattern size was approximately 470 × 470 mm. Each MTS trial involved a video screen display of three stimulus patterns as illustrated in Fig. 1. The "sample" stimulus of 32 randomly selected squares was displayed in the top center portion of the screen. Simultaneously presented below the sample were two comparison stimuli; one was a copy of the sample (the "matching stimulus") and one was different from the sample (the "nonmatching stimulus"). By randomly varying the position of 1, 2, 4, 8, 12, or 16 of the sample squares, the nonmatching stimulus



NON-MATCHING STIMULUS CONDITIONS

No. Squares Different	% difference
1/32	3.125
2/32	6.25
4/32	12.5
8/32	25.0
16/32	50.0

FIG. 1. Apparatus and task illustration. Shown is an illustration of the video display and response manipulanda. Nonmatching stimulus conditions were varied by changing the position of from 1 to 16 of the 32 little squares comprising the sample and matching stimuli.

was 3.125, 6.25, 12.5, 25, 37.5, or 50 percent different, respectively, from the sample and matching stimuli (see Fig. 1).

MTS Task

Each MTS response trial began with the video display of the sample and two comparison stimuli and ended with a subject button press on a three-button manipulanda. Subjects responded on the left or right buttons to indicate which of the two comparison stimuli (i.e., left or right) was the same as the sample. Either a left or right response cleared the video display and resulted in an intertrial interval of approximately 1 sec in duration. Correct matching responses also resulted in a 0.5-sec tone to provide correct response feedback. The center button had no programmed consequence. With each discrete trial, a new sample stimulus pattern was randomly generated and the position (left or right) of the nonmatching stimulus was randomly determined. The MTS task was performed as a multiple component schedule consisting of fifteen 60-sec components each separated by a 15-sec time-out. Across these fifteen components, the nonmatching stimulus condition (i.e., the percentage difference of the nonmatching stimulus) was systematically varied. During each component, the nonmatching stimulus condition was maintained constant. Across the fifteen components, five different nonmatching stimulus conditions were tested within each of three random block sequences. All subjects were exposed to the four nonmatching stimulus conditions in which the nonmatching stimulus was 3.125, 6.25, 12.5 and 25 percent different from the sample. With four subjects (S326, S334, S344 and S350), the fifth nonmatching stimulus condition was 37.5% different and for the remaining subjects it was 50% different from the sample. The task began with the screen message, "press any button to begin"; a "please wait" message appeared on the screen during the intercomponent time-out periods; and a "your session is complete" message was displayed at the end of the task which took approximately 22 min to complete. Since each component of the MTS task was 60 sec in duration, both response rate and the number of trials were dependent variables controlled by the subject's behavior. For each component, the data were the number of attempted and correct responses, the percentage correct (accuracy), and the number of points earned (correct minus errors). Additionally, the data were summed and averaged for overall performance across the different nonmatching stimulus conditions or were summed across the three blocks and averaged for performance under each nonmatching stimulus condition.

Monetary Reinforcement for MTS Performance

The first subject (S326) was instructed that his earnings were based solely upon the total number of correct responses. This subject maintained very accurate levels of performance throughout the study and completed the entire experiment under this payment contingency. A subsequent subject (not reported here) began to respond at high rates and with reduced accuracies approaching random responding (i.e., 50% accuracy) under those payment contingencies. Therefore, all remaining subjects were instructed that they would be "paid for each point derived as the total number of correct responses minus the number of errors." Under this payment contingency, both speed and accuracy were important determinates of monetary earnings. All subjects were paid daily based on the number of points earned on the MTS task which ranged from $19–27 under baseline conditions.

Digit-Symbol-Substitution Task (DSST)

This computerized task has been used extensively in previous studies (6, 16, 17). Briefly, subjects typed positions on a numeric keypad to reproduce symbol patterns simultaneously displayed on the video screen. The score was the number of correct responses during a 90-sec period.

Subject Ratings

Subjects rated the magnitude of perceived drug effects using a 5-point scale (0–4, labeled from "not at all" to "extremely") to indicate the magnitude of drug-induced effect, sleepiness and drug liking. These rating scales have been used previously (6).

Data Analysis

All data were the raw scores collected at each time-point before and after drug administration. The postdrug scores from selected data were expressed as a percentage of the predrug observation to equate for between subject differences. MTS data were statistically analyzed by repeated measures ANOVAs which accounted for the fixed factors of day (acquisition) or dose (drug data), time of day, block, and nonmatching stimulus condition. MTS time course data also compared TZ and LZ by including a "drug" factor. Only p values between 0.001 and 0.10 are reported. Selected analyses made multiple comparisons of the drug doses to the placebo control using Dunnett's tests ($p<0.05$). Polynomial regression analyses were conducted on placebo data to examine the linear, quadratic and cubic components of the nonmatching

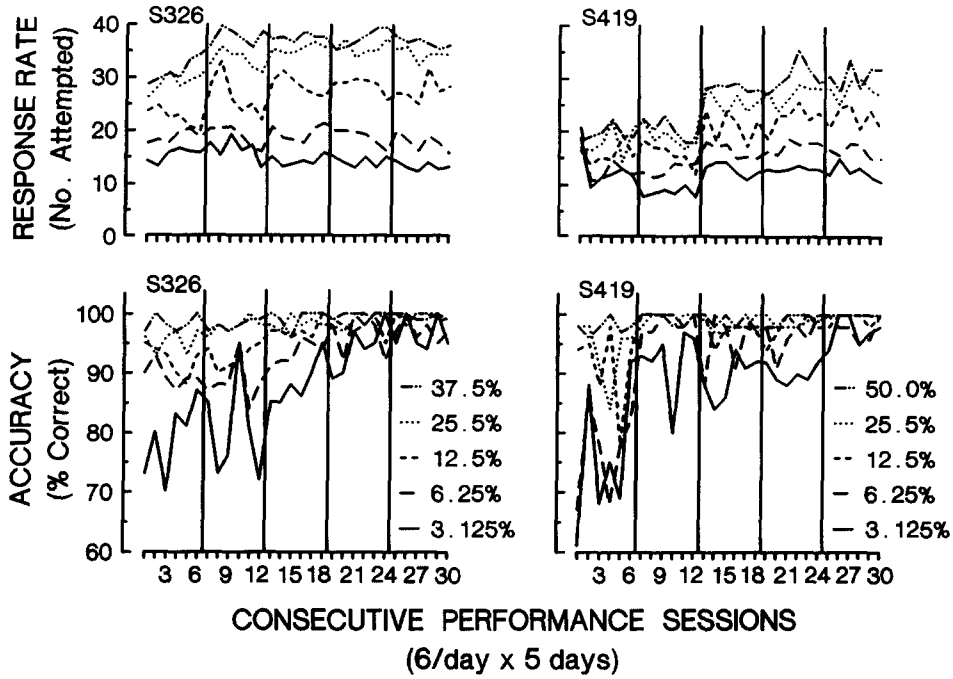


FIG. 2. MTS performance response rates (upper panels) and accuracy (lower panels) as a function of the nonmatching stimulus condition in two subjects (S326 and S419) during the five-day acquisition period. Data points are means of three block determinations per session for each of the six sessions per day across the first five days of MTS performance. Side legends on the lower panels show the nonmatching stimulus conditions expressed as the percentage of difference from the sample pattern.

stimulus condition-response functions.

RESULTS

MTS Performance Acquisition

Figure 2 shows MTS performance acquisition over the first five days of participation for the first (S326) and last (S419) subjects completing the experiment. These data generally are representative of those observed with other subjects. The upper panels show that the number of attempted responses were an orderly function of the nonmatching stimulus condition. Larger difference nonmatching stimulus conditions resulted in higher rates of responding. Response rates generally increased over days although this was predominately true for the nonmatching stimulus conditions of 12.5% or greater. Response rates were relatively stable by the fifth day of acquisition. The nonmatching stimulus conditions of 37.5% and 50% were not consistently different from the 25% nonmatching stimulus condition indicating a possible plateau in the nonmatching stimulus condition-response function as the differences become larger than 25%. Comparisons across subjects indicated that there were no consistent differences between the nonmatching stimulus conditions of 37.5% and 50% and therefore all subsequent analyses considered these conditions as equivalent and as representing the highest level of difference in the nonmatching stimulus condition. The lower panels of Fig. 2 show that the accuracy of responding also improved over the acquisition period and achieved high levels of accuracy ($\geq$95%) by the fifth day. The least different nonmatching stimulus conditions (e.g., 3.125% and 6.25%) produced the lowest accuracies and showed the most protracted acquisition function. Individual subject acquisition data were analyzed with ANOVAs by treating the block variable as a random factor thereby permitting three replicate determinations of each nonmatching stimulus condition at each time-point. These analyses of response rate and accuracy indicated that seven of the nine subjects exhibited the same basic acquisition patterns involving significant ($p<0.05$) main effects and interactions of days and nonmatching stimulus condition. Two subjects (S350 and S378) differed from this basic pattern in that they exhibited high accuracy performance uniformly across days and nonmatching stimulus conditions.

MTS performance under a particular nonmatching stimulus condition of the multiple component task was found to be independent of the preceding nonmatching stimulus condition (data not shown). Separately for each of the nine subjects and on their last day of acquisition, data from all six time-points was pooled to yield a mean response for a given nonmatching stimulus condition as a function of each of the other nonmatching stimulus conditions preceding it in the multiple component schedule. Data from all six time-points was pooled in order to get at least one observation of each nonmatching stimulus condition as a function of the preceding nonmatching stimulus condition. This was necessary since the nonmatching stimulus sequences were randomly determined within a block and each condition was not preceded by every other nonmatching stimulus condition on each occasion of task performance. For both the number of attempted responses and the percent correct, ANOVAs conducted on the data from all nine subjects showed significant main effects of nonmatching stimulus condition ($p<0.02$) but no main effects of or interactions with the preceding nonmatching stimulus condition (all F-ratios $\leq$1.02).

Time Course of Drug Effects

Figure 3 shows the time course of TZ and LZ effects on MTS

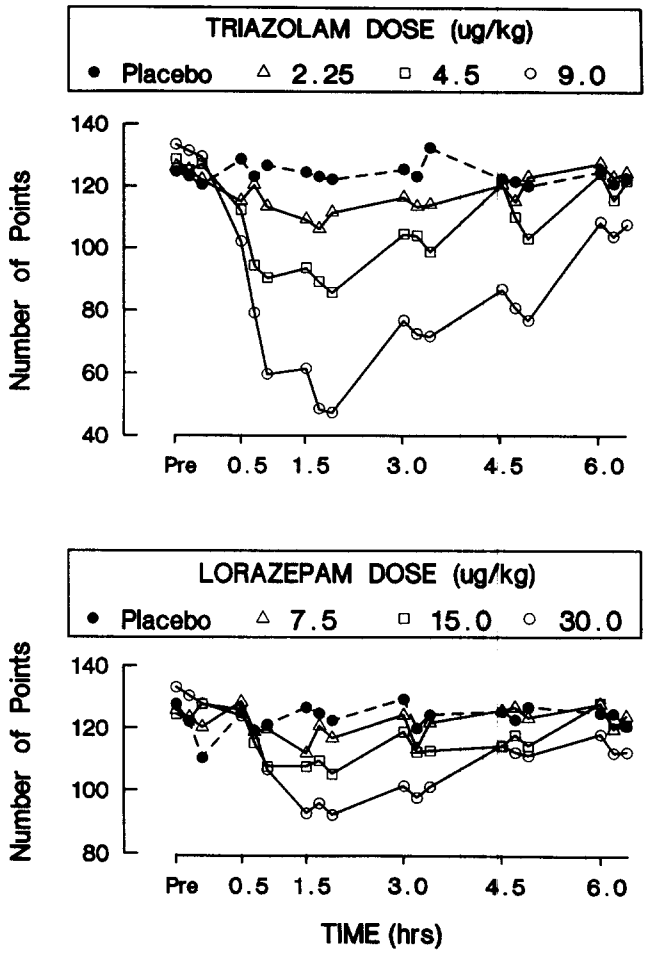


FIG. 3. Time course of triazolam and lorazepam dose effects on MTS performance. Shown are the number of points earned in each of three blocks per time-point occurring before (Pre) and at the indicated times after drug administration. The number of points are sums across the five nonmatching stimulus conditions presented within each block. Data points are means of seven subjects (triazolam) or six subjects (lorazepam). Triazolam and lorazepam doses (μg/kg) are indicated above each panel.

performance in each of the three blocks across the six time-points of the day. The number of MTS points earned are presented as an overall index of performance reflecting both response rate and accuracy. For both drugs, onset of effects was observed at 0.5 hr and peak effects were observed at 1.5 hr postdrug; thereafter, drug effects dissipated and returned towards predrug levels of performance. Significant ($p<0.001$) dose- and time-related effects of TZ were detected as main effects and an interaction of these variables. The block variable also produced significant ($p<0.05$) main effects and two- and three-factor interactions with the dose and time variables. These block effects are accounted for by two effects observed with the 4.5 and 9.0 μg/kg but not the 2.25 μg/kg or placebo doses. First, an onset of TZ effects was clearly observed as a progressive decrease in MTS performance across the three blocks at 0.5 hr postdrug. Second, decreased scores across the three blocks at the 1.5-, 3.0- and 4.5-hr time-points indicates that a general deterioration in performance occurred within the 22-min period of continuous MTS performance at each of these task sessions. Analysis of LZ effects also detected significant ($p<0.01$) main effects and an interaction of the dose and time variables. With LZ the only significant effect of blocks was a block × time interaction, $F(10,50)=2.52$, $p<0.025$, which is primarily accounted for by the decreased scores across the three blocks observed at 0.5 hr but not consistently observed at the other time-points. Comparisons of the effects of TZ and LZ clearly show that the highest LZ dose produced effects comparable to those of 4.5 μg/kg TZ while the highest TZ dose produced much larger effects. An ANOVA, comparing TZ and LZ in the six subjects who received the indicated doses of both drugs, detected an nonsignificant drug × dose level interaction, $F(3,15)=2.67$, $p<0.10$, and a significant drug × time interaction, $F(5,25)=5.37$, $p<0.005$, predominately due to the more robust effects observed with the highest TZ dose.

This basic time course of drug effects was also observed with the other measures including the subject ratings, and DSST performance (peak DSST impairment was observed at the 2.0-hr time-point). In the six subjects who received both drugs, 9.0 μg/kg TZ also produced larger effects than 30 μg/kg LZ on the DSST task and the subject ratings.

Individual Subject Patterns

Figure 4 shows the individual subject dose-response functions for the effects of TZ and LZ on MTS responding. With TZ, all subjects showed dose-related decreases in the number of attempted responses and all but S378 showed decreases in accuracy; usually only at the highest dose. For all subjects except S334, response rates were decreased at lower doses than those decreasing accuracy. The darkened symbols show that placebo levels of response were recovered after completing the ascending dose series. With LZ, doses up to 30 μg/kg generally produced modest response rate decreases in some subjects and had little effect on accuracy. In the last three subjects who received LZ doses up to 45 μg/kg, decreases in response rate and accuracy were more reliably observed. Comparisons of the effects of TZ and LZ showed that the selected LZ doses uniformly produced less effect than observed in the same subjects with TZ except for the response rate measure in S350 where LZ produced larger effects. Subjects S334 and S378 showed an atypical response to LZ in that response rates were increased with corresponding decreases in accuracy. This atypical response pattern may have been influenced by the fact that these subjects began to show an increasing trend in their response rates through the LZ dose-response sequence. This increasing trend can be seen in that their initial placebo response rates were greater than 100% predrug. However, an unstable baseline of increasing response rate may not completely account for the atypical LZ response since the same effect of LZ was replicated in S378 approximately two weeks later (data not shown) after his response rate had stabilized at a new higher rate.

MTS Performance as a Function of Nonmatching Stimulus Condition

Figure 5 shows the effects of placebo and TZ on response rate and accuracy as a function of the nonmatching stimulus condition. ANOVAs were conducted on the placebo data alone to examine the effects of the nonmatching stimulus condition on MTS performance in the absence of drug effects. Both response rate, $F(4,24)=65.39$, $p<0.001$, and accuracy, $F(4,24)=3.98$, $p<0.02$, increased as a positive function of the difference in the nonmatching stimulus condition. Polynomial regression analysis showed that the nonmatching stimulus function on response rate was strictly linear ($p<0.001$) but the effect on accuracy had a significant quadratic component ($p<0.05$). The nonlinear component in the accuracy data was due to the reduced accuracy performance observed with the 3.125% (mean = 92.4%) and 6.25% (mean =

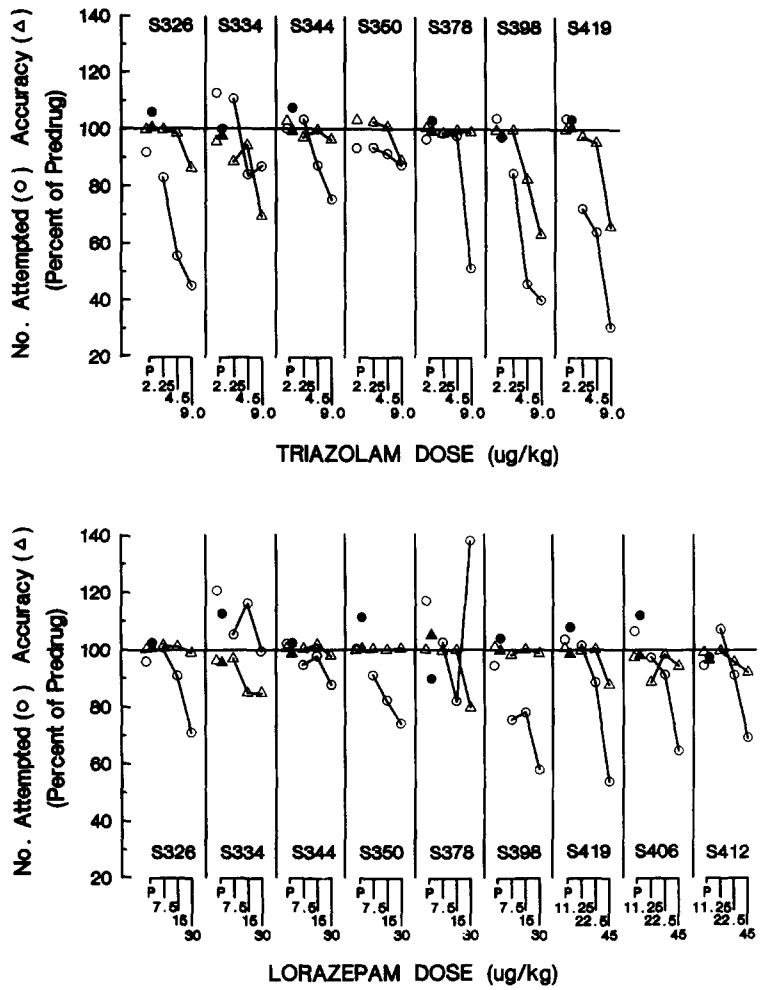


FIG. 4. Individual subject MTS performance as a function of triazolam and lorazepam dose. Shown are the total number attempted and the total percent correct summing across all components and nonmatching stimulus conditions. Data are observations at 1.5 hr following drug administration and are expressed as a percentage of the predrug observation. Dosages are μg/kg body weight and "P" designates placebo; darkened symbols represent placebo observations replicated after the ascending dose series was completed.

93.6%) nonmatching stimulus conditions relative to the other nonmatching stimulus conditions (overall mean = 98.1%).

Effects of TZ as a Function of Nonmatching Stimulus Condition

Figure 5 also shows that the effects of TZ were influenced by the nonmatching stimulus condition. An ANOVA conducted on the response rate data showed significant effects of dose, $F(3,18) = 13.64$, $p<0.001$, nonmatching stimulus condition, $F(4,24) = 93.04$, $p<0.001$, and a dose × nonmatching stimulus interaction, $F(12,72) = 5.21$, $p<0.001$, but no block main effects or interactions with the other variables. Post hoc testing showed that TZ produced dose-related decreases in response rate which were significant only with the higher response rates observed when the nonmatching stimulus conditions were 12.5% or greater. Only modest, nonsignificant effects were observed on the low response rates engendered with nonmatching stimulus conditions less than 12.5%. The ANOVA conducted on the accuracy data also showed an effect of dose, $F(3,18) = 9.43$, $p<0.001$, and nonmatching stimulus condition, $F(4,24) = 14.40$, $p<0.001$. Whereas lower doses of TZ tended to reduce accuracy, significant effects were achieved only with the highest dose and this occurred across all nonmatching stimulus conditions. The magnitude of the TZ-induced decrease in accuracy appeared to be inversely related to the degree of difference in the nonmatching stimulus; however, the dose × nonmatching stimulus condition interaction was not significant, $F(12,72) = 1.88$, $p<0.10$. Inspection of the individual subject data (not shown) revealed that five of the seven subjects indeed showed greater effects of TZ at the 3.125% nonmatching stimulus condition than at the 50% condition.

Effects of LZ as a Function of Nonmatching Stimulus Condition

Statistical analysis of LZ effects were conducted only in the first six subjects who received doses up to 30 μg/kg. As before, the nonmatching stimulus condition produced main effects on response rate, $F(4,20) = 46.08$, $p<0.001$, and accuracy, $F(4,20) = 5.46$, $p<0.005$. However, the only significant effect of LZ was a

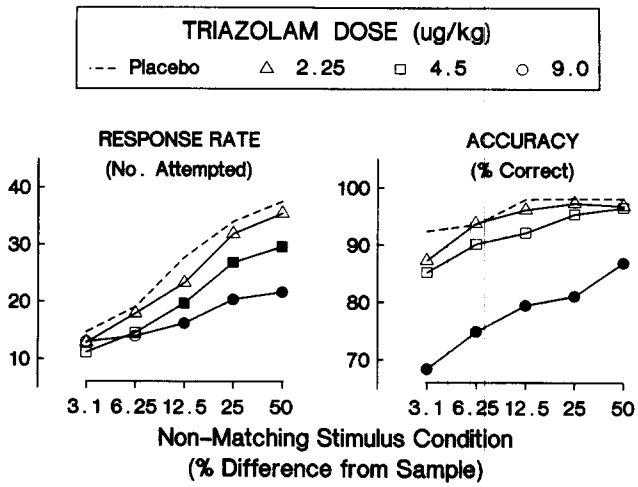


FIG. 5. Triazolam dose effects on MTS performance as a function of the nonmatching stimulus condition. Shown are the number attempted and the percent correct at each nonmatching stimulus condition. Data are means of seven subjects and three block determinations observed at 1.5 hr following drug administration. Doses are μg/kg body weight. The nonmatching stimulus condition labeled as 50% actually collapses data from four subjects at nonmatching stimulus = 37.5% and three subjects at nonmatching stimulus = 50%. Darkened symbols indicate significant ($p<0.05$) difference from placebo using Dunnett's Multiple Comparisons to a Control procedure.

dose × nonmatching stimulus interaction, $F(12,60)=2.24$, $p<0.025$, on response rate. This interaction was due to modest LZ-induced decreases in response rate which only occurred at the larger difference nonmatching stimulus conditions. At these doses, no significant effects of LZ on MTS performance accuracy were detected.

DISCUSSION

This paper has reported the initial results obtained with a newly developed visual pattern MTS task. Under nondrug conditions, response rates increased as an orderly log-linear function of the percent difference between the matching and nonmatching stimuli. Inasmuch as task performance was time-limited and the financial payment contingencies encouraged high rate/accurate performance, these data reasonably indicate a linear functional relationship between response rate and the "discriminability" of the matching and nonmatching stimuli. Accuracy was also a positive function of the discriminability of the nonmatching stimuli. However, this effect was quite modest due to the high degree of stimulus control (i.e., 92–98% accuracy) observed across all nonmatching stimulus conditions. The reduced accuracies observed when the nonmatching stimuli were <12.5% different from the sample indicates that responses under these conditions were under less tight stimulus control than when the nonmatching stimuli were more discriminable. The nonlinear shape of the functional relation between accuracy and nonmatching stimulus condition also suggests the possible involvement of multiple factors which differentially affect accuracy as a function of nonmatching stimulus discriminability.

This MTS task differs from most reported MTS procedures in three ways. First, randomly generated sample and nonmatching stimulus patterns were presented so that each discrete trial involved unique sets of stimuli; stimuli were not repeated across trials. Second, across each trial within a 60-sec component, the nonmatching stimulus was a constant percentage difference from the sample and matching stimuli. However, across components, the percentage difference of the nonmatching stimulus was systematically varied as an independent variable. Third, performance within each component was time-limited so that response rates and the number of trials were dependent measures. Most MTS procedures have employed only a few easily discriminable stimuli varying in color (1, 2, 8) or geometric symbol type (10) and have repeatedly presented the same stimuli over a fixed number of trials. Whereas studies of stimulus generalization have systematically varied stimulus discriminability (5), this has been done less frequently in MTS procedures (24). Human studies of MTS performance also have employed a few stimuli discriminable by color (23) or geometric shape (19). Sidman (15,20) examined stimulus generalization and stimulus control phenomena in simultaneous and delayed-MTS responding in humans by using eight different comparison stimuli which varied either in line orientation or in ellipticity. Sample stimulus control was generally good under the simultaneous MTS and short delay conditions and the frequency of responding was positively related to the degree of similarity between the sample and nonmatching stimuli.

In the present study, TZ produced dose-related decreases in the response rate and accuracy of MTS performance. Rate-decreasing effects of TZ were consistently observed at lower doses than those affecting accuracy. These results indicate that rate suppressant effects of TZ are separable from and occur at lower doses than its effect to disrupt stimulus control. However, rate-decreasing effects of TZ were only significant at the higher response rate, easier discrimination conditions and were not observed when the nonmatching stimuli were less than 12.5% different from the sample. These results are consistent with conclusions that benzodiazepines are more likely to impair human performance in tasks involving rapid responding (25) and that speed is more readily affected than accuracy (3).

MTS accuracy was significantly decreased only with the highest TZ dose (9.0 μg/kg) and this effect occurred across all levels of nonmatching stimulus discriminability. Whereas accuracy decreases tended to be larger and occur at lower TZ doses with the least discriminable nonmatching stimulus condition, these effects were not significant. These results suggest that only relatively high doses of TZ disrupted the tight stimulus control observed in this simultaneous MTS procedure and that stimulus discriminability did not significantly influence this disruption. In delayed-MTS procedures, benzodiazepines have been reported to decrease accuracy at doses equal to or less than those affecting response rates (13,14). In those procedures, however, reinforcement was contingent on accuracy, not response rate. Also, the use of temporal delays between the sample and comparison stimuli is known to reduce the degree of stimulus control (15,22) and enhances the sensitivity of the procedure to detect drug-induced reductions in accuracy (8). In contrast, the present study involved a payment contingency "incentive" on high response rates and the simultaneous presentation of sample and comparison stimuli resulted in tight stimulus control.

The present study also reported TZ dose-related decreases in DSST performance and increases in subject ratings of drug effects indicating that these dose-effects were consistent with those previously reported to impair human performance (6). The TZ doses of 2.25, 4.5 and 9.0 μg/kg (equivalent to 0.16, 0.32 and 0.63 mg/70 kg) encompass the usual therapeutic range for TZ where the recommended hypnotic doses are 0.125–0.5 mg per person (12). TZ was compared to LZ in the present study to determine whether the observed effects of TZ might generalize to other benzodiazepines. LZ doses of 7.5, 15.0 and 30.0 μg/kg (equivalent to 0.53, 1.05 and 2.1 mg/70 kg) produced less effect than observed with TZ. In three subjects, LZ doses were increased by 50% so that the high dose was 45.0 μg/kg (3.2 mg/70 kg). This higher LZ dose is closer to those recommended therapeutically

(12) and produced effects on MTS performance more comparable to those observed with TZ. Thus, it is likely that LZ would have produced effects more similar to TZ if higher doses had been used.

The TZ-induced impairments of MTS performance could be due to drug effects on a variety of processes. Benzodiazepines are known to decrease oculomotor function (18) and visual threshold for light detection (7). In addition to possible sensory-motor disturbance, benzodiazepines have been shown to decrease performance on a variety of psychomotor performance tasks (3,25). Analyses of these performance impairments has generally yielded the conclusion that benzodiazepines impair attention, reaction time and motor coordination and that response speed is more readily affected than accuracy (3,25). Previous studies of benzodiazepine effects on MTS performance in nonhuman subjects have employed the delayed-MTS paradigm (9, 10, 13, 14) and have reported that benzodiazepine-induced disruptions increase with the length of the delay interval (10). To our knowledge, the present study is the first to examine benzodiazepine effects on human MTS behavior and to report drug-induced disruptions of stimulus control with simultaneous MTS procedures.

Further studies with this MTS procedure should provide useful information on the role of drug-induced changes in environmental stimulus control as it relates to drug-induced impairment of human performance. The advantages of this procedure include: 1) good quantitative control of visual stimulus patterns and the discriminability of nonmatching stimuli; 2) the ability to vary discrimination difficulty and baseline response rates within a session of task performance; and 3) the ability to clearly separate drug-induced changes in response rate and accuracy and how these effects vary as a function of task difficulty.

REFERENCES

1. Berryman, R.; Cumming, W. W.; Nevin, J. A.; Jarvik, M. E. Effects of sodium pentobarbital on complex operant discriminations. Psychopharmacologia 6:388–398; 1964.
2. Berryman, R.; Jarvik, M. E.; Nevin, J. A. Effects of pentobarbital, lysergic acid diethylamide and chlorpromazine on matching behavior in the pigeon. Psychopharmacologia 3:60–65; 1962.
3. Cole, S. O. Effects of benzodiazepines on acquisition and performance: A critical assessment. Neurosci. Biobehav. Rev. 10:265–272; 1986.
4. Diagnostic and statistical manual of mental disorders, 3rd ed., revised (DSM III-R). Washington, DC: American Psychiatric Association; 1987.
5. Honig, W. K.; Urcuioli, P. J. The legacy of Guttman and Kalish (1956): 25 years of research on stimulus generalization. J. Exp. Anal. Behav. 36:405–445; 1981.
6. Kirk, T.; Roache, J. D.; Griffiths, R. R. Dose-response evaluation of the amnestic effects of triazolam and pentobarbital in normal subjects. J. Clin. Psychopharmacol.; in press.
7. Lukas, S. E.; Hienz, R. D.; Brady, J. V. Effects of diazepam and triazolam on auditory and visual thresholds and reaction times in the baboon. Psychopharmacology (Berlin) 87:167–172; 1985.
8. McMillan, D. E. Effects of chemicals on delayed matching behavior in pigeons I: Acute effects of drugs. Neurotoxicology 2:485–498; 1981.
9. McMillan, D. E. Effects of chemicals on delayed matching behavior in pigeons II: Tolerance to the effects of diazepam and cross tolerance to phencyclidine. Neurotoxicology 3:138–141; 1982.
10. Nicholson, A. N.; Wright, C. M. Inhibitory and disinhibitory effects of nitrazepam, diazepam and flurazepam hydrochloride on delayed matching behavior in monkeys (Macaca mulatta). Neuropharmacology 13:919–926; 1974.
11. Nicholson, A. N.; Wright, C. M.; Ferres, H. M. Impaired performance on delayed matching in monkeys by heptabarbitone, pentobarbitone sodium and quinalbarbitone sodium. Neuropharmacology 12: 311–317; 1973.
12. Physician's desk reference, 43rd ed. Oradell, NJ: Medical Economics Company, Inc.; 1989.
13. Picker, M.; White, W.; Poling, A. Effects of phenobarbital, clonazepam, valproic acid, ethosuximide, and phenytoin on the delayed matching-to-sample performance of pigeons. Psychopharmacology (Berlin) 86:494–498; 1985.
14. Poling, A.; Picker, M.; Vande Polder, D.; Clark, R. Chronic effects of ethosuximide, phenytoin, clonazepam, and valproic acid on the delayed-matching-to-sample performance of pigeons. Psychopharmacology (Berlin) 88:301–304; 1986.
15. Ray, B. A.; Sidman, M. Reinforcement schedules and stimulus control. In: Schoenfeld, W. N., ed. The theory of reinforcement schedules. New York: Appleton-Century-Crofts, Meredith Corp.; 1970:187–214.
16. Roache, J. D.; Griffiths, R. R. Interactions of diazepam and caffeine: Behavioral and subjective dose effects in humans. Pharmacol. Biochem. Behav. 26:801–812; 1987.
17. Roache, J. D.; Griffiths, R. R. Lorazepam and meprobamate dose effects in humans: Behavioral effects and abuse liability. J. Pharmacol. Exp. Ther. 243:978–988; 1987.
18. Rothenberg, S. J.; Selkoe, D. Specific oculomotor deficit after diazepam I. Saccadic eye movements. Psychopharmacology (Berlin) 74:232–236; 1981.
19. Saunders, K. J.; Spradlin, J. E. Conditional discrimination in mentally retarded adults: The effect of training the component simple discriminations. J. Exp. Anal. Behav. 52:1–12; 1989.
20. Sidman, M. Generalization gradients and stimulus control in delayed matching to sample. J. Exp. Anal. Behav. 12:745–757; 1969.
21. Spitzer, R. L.; Endicott, J. Schedule for affective disorders and schizophrenia—Life-time version (SADS-L), 3rd ed. New York: State Psychiatric Institute, Biometrics Research; 1978.
22. Thompson, D. M. Stimulus control and drug effects. In: Blackman, D. E.; Sanger, D. J., eds. Contemporary research in behavioral pharmacology. New York: Plenum Press; 1978:159–207.
23. Torgrud, L. J.; Holborn, S. W. Effectiveness and persistence of precurrent meditating behavior in delayed matching to sample and oddity matching with children. J. Exp. Anal. Behav. 52:181–191; 1989.
24. Wright, A. A.; Sands, S. F. A model of detection and decision processes during matching to sample by pigeons: Performance with 88 different wavelengths in delayed and simultaneous matching tasks. J. Exp. Psychol.: Anim. Behav. Proc. 7:191–216; 1981.
25. Woods, J. H.; Katz, J. L.; Winger, G. Abuse liability of benzodiazepines. Pharmacol. Rev. 39:251–419; 1987.